THE SUPPRESSION OF THE HALLER-BAUER SCISSION FOR SYNTHETIC PURPOSES

THESIS
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BY

S. M. VINES, B.Sc.

DEPARTMENT OF CHEMISTRY
BROCK UNIVERSITY, ST. CATHARINES, ONTARIO
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TO MY PARENTS
I sincerely acknowledge the great debt of gratitude I owe to Dr. M. S. Gibson, for his guidance and advice throughout the course of my research work and the preparation of this thesis.

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ABSTRACT
ABSTRACT

A number of 2-chlorobenzophenones, containing electron releasing groups (e.g. hydroxy, thiomethoxy and methoxy) in the 4'-position, were prepared by the Friess rearrangement, or the Friedel-Crafts reaction. These ketones, when treated with potassamide in liquid ammonia, underwent partial Haller-Bauer scission, unlike 2-chlorobenzophenone which is known to undergo complete scission.

Under similar conditions 4-nitrobenzophenone also underwent partial scission, but the main reaction in this case was nucleophilic amination of the nitro containing ring. This amination reaction was shown not to be a useful general reaction for aromatic nitro compounds.

3-Methylxanthone was then prepared by treatment of 2- and 3-chloro-2'-hydroxy-5'-methylbenzophenone with little, if any, attendant scission. The corresponding 2-fluoro compound also gave the xanthone, but as the 3-fluoro compound did not, it was concluded that the 2-fluoro compound reacted through a nucleophilic substitution mechanism, rather than the benzyne mechanism invoked for the chloro and bromo compounds.

3-Methylthioxanthone was synthesised by treatment of methyl 4-tolyl sulphide and 2-chlorobenzoyl chloride with aluminum chloride in carbon disulphide, followed by heating. This compound was also prepared by treatment of 3-chloro-2'-thiomethoxy-5'-methylbenzophenone with potassamide in liquid ammonia.
INTRODUCTION
THE HALLER-BAUER SCISSION

The Haller-Bauer scission reaction involves the splitting of a non-enolisable ketone, by amide ion, to give an amide and a hydrocarbon.

\[ R - C - R' \xrightarrow{\text{NH}_2^-} R' + H_2N \cdot C \cdot R' \]

Enolisation is a form of tautomerism involving, in the simplest case, reversible transfer of a proton to the oxygen atom of a carbonyl group, from an adjacent carbon atom.

\[ R \cdot CH_2 \cdot C \cdot R' \rightleftharpoons R \cdot CH = C \cdot R' \]

Keto structure  Enol structure

Ketones may be non-enolisable for two reasons. If, for example, no hydrogen atoms are attached to the \( \alpha \)-carbon atoms, as in di-t-butylketone (I), benzophenone (II) or 2,2,5,5-tetramethylpentanone (III), then an enol can not be formed. If the carbonyl group is adjacent to a bridgehead carbon atom, as in camphorilone (IV), an enol can not be formed, as the double bond required for the enol can not be accommodated in the rigid carbon framework.

\[ \text{(I)} \]

\[ \text{(II)} \]

\[ \text{(III)} \]

\[ \text{(IV)} \]
Enolisation is however possible if the substituents around the enolic double bond are in a planar or near coplanar arrangement, as in the decalone shown below.

The cleavage of non-enolisable ketones by sodamide was discovered by Semmler\(^1\), in 1906. He was investigating the structure of fenchone (V).

He did not investigate the reaction further. This was left to Haller and Bauer, who observed the formation of benzamide when benzophenone is treated with sodamide in boiling benzene or toluene\(^2\).

\[
\text{Ph} - \overset{0}{\text{C}} - \text{Ph} \xrightarrow{\text{NaNH}_2} \text{Ph} - \overset{0}{\text{C}} - \text{NH}_2 + \text{PhH}
\]

Since that time ketones (II)\(^3\), (III)\(^4\) and (IV)\(^5\) have been shown to undergo the reaction.

\[
(\text{CH}_3)_3\overset{0}{\text{C}} - \overset{0}{\text{C}(\text{CH}_3)}_3 \xrightarrow{\text{NaNH}_2} (\text{CH}_3)_3\overset{0}{\text{C}} - \overset{0}{\text{NH}_2}
\]

\[
\xrightarrow{\text{Me}} (\text{CH}_3)_2\overset{0}{\text{CH} - \overset{0}{\text{CH}_2 - \overset{0}{\text{CH}_2 - \overset{0}{\text{C}(\text{CH}_3)}_2 - \text{CNH}_2}}
\]

\[
\xrightarrow{\text{Me}} \overset{0}{\text{CONH}_2}
\]
Haller and Bauer proposed a mechanism for the reaction, that is basically still acceptable today.

\[
\begin{align*}
R - C - R' & \xrightarrow{\text{NH}_2} R - C - R' \xrightleftharpoons{\text{H}_2} R - C = O + R' \\
\text{(VI)} \quad \text{(VII)}
\end{align*}
\]

When \( R = R' = \text{Ph} \), intermediate (VI) is isolable\(^2\). On treatment with water, this gives benzamide and benzene.

4-Phenylbenzophenone gives a precipitate on treatment with sodamide in dry refluxing toluene. If the precipitate is filtered off, biphenyl can be isolated from the filtrate\(^6\). This is a strong piece of evidence for the intermediary of ion (VII).

Many ketones have been split under these conditions\(^7\). The work of Lea and Robinson\(^8\), and of Schönberg\(^9\) showed that a ketone R\(_3\)OR' will be split, so that the main products are amide R'CONH\(_2\) and hydrocarbon R-H, if R' is more strongly electron repelling than R. This adds further weight to the proposed mechanism. Scission of a number of unsymmetrical diaryl ketones, shown in table (I), clearly demonstrates this.
TABLE I
THE HIGH TEMPERATURE HALLER-BAUER SCISSION

\[
\begin{align*}
\text{O} & \xrightarrow{\frac{1}{2} \text{NaNH}_2, 2 \cdot \text{H}^+} \text{CO}_2\text{H} \\
\text{X} & \quad \text{Cl} & \quad \text{Br} & \quad \text{OMe} & \quad \text{OMe} & \quad \text{NMe}_2
\end{align*}
\]

\[
\begin{align*}
\text{X} & \quad \% \text{ of (IX)} & \quad \% \text{ of (VIII)} \quad \text{Ref.} \\
\text{Cl} & \quad 16 - 34 & \quad 66 - 84 \quad 9 \\
\text{Br} & \quad 15 - 40 & \quad 60 - 85 \quad 9 \\
\text{OMe} & \quad 52.8 - 68.4 & \quad 31.6 - 47.2 \quad 9 \\
\text{OMe} & \quad 67.1 & \quad 32.9 \quad 8 \\
\text{NMe}_2 & \quad 55.2 & \quad 44.8 \quad 9
\end{align*}
\]

Chlorine and bromine are inductively electron attracting and mesomerically electron releasing. The methoxy group and the dimethylamino group also exhibit these effects in the same direction. Chlorine and bromine both encourage formation of benzoic acid, showing that the inductive effect is more important in stabilising the halogenophenyl ion, with respect to the phenyl anion. The methoxy group and the dimethylamino group both encourage formation of the substituted benzoic acid, suggesting that the mesomeric effect is relatively strong and the inductive effect is relatively weak. This destabilises the substituted anion. The relative strengths of the inductive and mesomeric effects observed here are in accordance with many other experimental results.
RING CLOSURE THROUGH BENZYNE INTERMEDIATES

Benzyne or 1,2-dehydrobenzene has been known through its reactions for many years. Our chemical ancestors noticed rearrangements occurring in reactions that are known today to involve benzyne intermediates, such as the reaction occurring when arnesulphonates are fused with alkali, which was first examined around 1870.

Rearrangements in the amination of aryl halides were observed, and research into these reactions culminated in a clear demonstration of the existence of benzyynes\textsuperscript{10}. Today a variety of paths to benzyne intermediates are known, many of which do not require the harsh, basic conditions previously resorted to.

Several reviews have appeared on the subject of benzyne chemistry. A good introduction to the subject is provided by a review, written by Bunnett\textsuperscript{11}. More recently a comprehensive monograph has appeared on the subject\textsuperscript{12}.

One of the easiest routes to benzyne intermediates, and the one of concern here, involves the metallation of aryl halides. When an electronegative entity is placed into a benzene ring, the 2-hydrogens become the most acidic. If various benzene derivatives (such as fluorobenzene, trifluoromethylbenzene and methoxybenzene) are deuterated, and treated with potassamide in liquid ammonia, exchange is found to be fastest at the 2-position and slowest at the 4-position. Deuterobenzene and deuterotoluene exchange too slowly for convenient measurement\textsuperscript{13}. This work is one of the best demonstrations of the acidity of such hydrogen atoms.
If the electronegative group present is a halogen, then the 2-halogenophenyl anion, formed by loss of a proton, may lose halide ion, to give a benzyne.

![Chemical structure diagram]

The benzyne, once produced, can react with nucleophiles. If amide ion is present in the mixture used to generate the benzyne, then this may act as the trapping agent; hence chlorobenzene will react with potassamide in liquid ammonia to give aniline\(^\text{10}\).

![Chemical structure diagram]

Alternatively a nucleophilic site may be built into the aryl halide so that a new ring is produced in the molecule by successful attack.

![Chemical structure diagram]
Several new syntheses of ring systems, including benzothiazoles and indoles, were developed using this technique\textsuperscript{14,15}.

\[
\begin{align*}
\text{Br} & \quad \text{S} \quad \text{NH}_{2} \quad \text{S} \\
\text{Cl} & \quad \text{O} \quad \text{CH}_{2} \quad \text{C} \quad \text{CH}_{3} \\
\text{NH} & \quad \text{C} \quad \text{O} \
\end{align*}
\]

Unfortunately there are limitations to this method, as are outlined by Bunnett et al\textsuperscript{15}. These are:

1. The substance subjected to the action of a strong base may be converted into an anion with such a high concentration of negative charge on an atom next to the ring, that aryne formation is prevented.

2. The side chain nucleophile may not be an effective competitor with the external base, due to inherently low nucleophilicity, or an unfavourable steric relationship to the aryne function.

3. The product of ring closure may react further with the external nucleophile.

4. The side chain may produce a different nucleophilic species from that expected.

5. An alternative reaction may occur. This will be discussed later.
TABLE II
The Action of Potassamide in Liquid Ammonia on Halogenobenzophenones

![Chemical structure of a halogenobenzophenone](image)

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>REACTION TIME (min.)</th>
<th>PRODUCTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>180</td>
<td>Starting material (98%)</td>
</tr>
<tr>
<td>Cl</td>
<td>H</td>
<td>H</td>
<td>20</td>
<td>(Benzoic acid (79%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Aniline (77%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Residual tar (14%)</td>
</tr>
<tr>
<td>F</td>
<td>H</td>
<td>H</td>
<td>15</td>
<td>Benzoic acid (96%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fluorobenzene (29%)</td>
</tr>
<tr>
<td>H</td>
<td>Cl</td>
<td>H</td>
<td>300</td>
<td>Benzoic acid (1.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Impure residue m.p. 130°(8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[Acetanilide? (6%)]</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>360</td>
<td>Benzoic acid (1.6%)</td>
</tr>
</tbody>
</table>
|    |    |    |                      | 2-aminobenzophenone (42%)
|    |    |    |                      | 3-aminobenzophenone (25%)
|    |    |    |                      | 3-aminobenzophenone (42.5%)
|    |    |    |                      | 4-aminobenzophenone (6.5%)
|    |    |    |                      | Residue (~ 20%)       |
6. Intermolecular reaction may occur, with the side chain of one molecule adding to the benzyne function of another.

Despite these drawbacks, it seems we have a useful synthetic technique involving benzyne intermediates, as a supplement to nucleophilic substitution. Despite the angular strain involved, four membered rings can be closed almost as readily as five or six membered rings\(^{16}\). Seven membered rings can be closed with slightly more difficulty\(^ {16}\), and even larger rings may be closed in reasonable yields, with the aid of dilution techniques\(^ {17}\).

The nucleophilic side chains involved in such ring closures, have had carbon, oxygen, nitrogen, and sulphur as the attacking atom.

**LOW-TEMPERATURE HALLER-BAUER SCISSION**

In 1962, Bunnett and Hrutfiord showed that benzophenone is not split by treatment with potassium in refluxing liquid ammonia (-33°). 2-Chlorobenzophenone, however, is readily split under these conditions\(^ {18}\). (See table II).

The reaction was rationalised in terms of the following sequence:-
Once the 2-chlorophenyl anion is formed, it can readily lose chloride ion to give benzyne (XIII), which will readily add ammonia to give aniline, one of the principal products.

The nature of the halogen present strongly affects the ease of benzyne formation. It is found that the order of reactivity of aryl halides with potassamide in liquid ammonia is \( \text{Br} > \text{I} > \text{Cl} > \text{F} \)\(^\text{19} \). This appears to be the result of two opposing factors. Since the order of electronegativities of the elements is \( \text{F} > \text{Cl} > \text{Br} > \text{I} \), the order of acidities of the 2-hydrogen atoms in the aryl halides will be the same. Opposed to this is the order of the halide ions with respect to their effectiveness as leaving groups. This is \( \text{I} > \text{Br} > \text{Cl} > \text{F} \). These two effects together result in the series obtained experimentally.

These observations explain why 2-chlorobenzophenone gives aniline as a principal product, whereas 2-fluorobenzophenone gives fluorobenzene. Once formed, the 2-fluoro-phenyl ion is protonated to give fluorobenzene, rather than losing fluoride ion, to give benzyne (XIII).

Intermediate (XI) is included in the reaction sequence mainly by analogy with the deformylation of aldehydes, initiated by hydroxide ion\(^\text{20} \).

It can be shown that the reaction is a two stage process, rather than a process involving concerted rupture of the C-C and C-Cl bonds. If 2-chloro-4-methylbenzophenone (XIV) is treated with potassamide under the same conditions, the products contain 2-toluidine. Concerted scission would produce 4-methylbenzyne (XVI), which would progress to 3- and 4-toluidines\(^\text{10} \), but no 2-toluidine. Stepwise scission
would give anion (XV) initially, which might expel chloride ion to give benzyne (XVI), or capture a proton to give 3-chlorotoluene from which all three toluidines can be formed. Bunnett and Hartrford were able to demonstrate the existence of 2-toluidine in the mixture, from its infrared spectrum, and also by isolating acet-2-toluidide by chromatography of the acylated mixture on alumina. The scission, therefore, can not be concerted.

3- and 4- Chlorobenzophenones both undergo little cleavage. Roberts and co-workers showed that when an aryl halide carries an inductively electron attracting substituent, a benzyne generated between positions 2 and 3 should give a 3-substituted product, and a benzyne generated between positions 3 and 4 should show a preference for a 4-substituted product. Where the aryl halide carries a group releasing electrons through induction, a benzyne formed between positions 2 and 3 would be expected to give predominantly the 2-substituted product, whereas a benzyne between the 3 and 4 positions ought to give preferentially the 3-substituted product. The situation is complicated for addition to the 4-position in a 3, 4-benzyne, since inductive effects are less strong in this position, and conjugative powers possessed by groups such as methoxy may become important. This rule has been used to explain the products obtained when 3- or
4-chlorobenzophenone is treated with potassamide in liquid ammonia.

Bunnett and Hrutfiord first tried to explain the reaction in terms of intermediates (XVII) and (XVIII).

![Chemical Structures](image)

It was assumed that the inductive effect of the benzoyl group is similar to that of the trifluoromethyl group. This would lead us to expect (XVII) to give mainly 3-aminobenzophenone, whereas (XVIII) should yield 4-aminobenzophenone and 3-aminobenzophenone in approximately equal quantities.

4-Chlorobenzophenone can only give (XVIII) and so should give the 3- and 4-substituted products in approximately equal parts. 3-Chlorobenzophenone yields no 4-aminobenzophenone, and so it was tentatively assumed that this compound does not react at all through intermediate (XVIII), despite the fact that one third of the starting material was not accounted for. This would lead us to expect 3-aminobenzophenone to be the main product.

Experiment shows that both 3- and 4-chlorobenzophenone add amide ion predominately at the position nearer to the carbonyl group (Table II); hence the mechanism proposed is untenable.

Bunnett and Hrutfiord then considered the possibility that intermediates (XIX) and (XX) are involved; these are formed by addition of amide ion to the carbonyl function to produce \(-\text{C}(\text{NH}_2)(\text{C}_6\text{H}_5)\text{C}^-\). This group
is electron releasing, and so according to Roberts' rule, should favour the addition to the benzene function at the position nearer to the substituent, which is observed \[\text{c.f. page (19)}\].

Walthew\textsuperscript{21}s suggests that Bunnett does not give sufficient weight to the inductive effects of the 2-, 3-, and 4- chlorine atoms in each of the cases considered. The effect upon the electron deficiency of the carbonyl group would be much greater, when the chlorine atom is in the 2- position, than when it is in the 3- or 4- position. As evidence he cites the acidities of the chlorobenzoic acids (2-chlorobenzoic acid, \(pK_a\) 2.89; 3-chlorobenzoic acid, 3.82; 4-chlorobenzoic acid, 4.03). As a result of this, for 2-chlorobenzophenone, one would expect easy attack of the nucleophile \(\text{NH}_2^-\) on the carbonyl carbon atom, making step \((a)\), in the formulation below, fast.

When the chlorine is in the 3- or 4- position, this activation will diminish, making step \((a)\) slower, hence the much greater reaction times.
Step (b) requires the formation of intermediate (XXI). This step is facilitated in the case of 2-chlorobenzophenone, because of the electronic inductive effect of the halogen; this is evidently not the case with 3- and 4- chlorobenzophenones, as little or no decomposition occurs.

Addition of amide ion to the carbonyl carbon of 3-chlorobenzophenone is somewhat more difficult than in the case of 2-chlorobenzophenone. However, this step must be occurring at an appreciable rate, for the observed products to be formed, unless a mechanism, first suggested by Bunnett and Hrutfiord\(^{18}\), is playing an important part in producing the 2-aminobenzophenone.

\[
\begin{align*}
(\text{XIX}) & \xrightarrow{\text{NH}_2} \text{C}_6\text{H}_5 \xrightarrow{\text{NH}_3} \text{O-} \text{C-} \text{NH} \xrightarrow{\text{etc.}} \text{C}_6\text{H}_5 \\
\end{align*}
\]

The products from 4-chlorobenzophenone were as predicted if one assumes that the benzyno intermediate carries an electron releasing \(-\text{C(NH}_2\text{)(C}_6\text{H}_5)0^-\) group; hence amide addition to the carbonyl carbon must still be occurring at an appreciable rate, so that step (c) is still important. The ratio of products shows that the reaction is occurring largely through intermediate (XX), since the presence of a free electron attracting carbonyl group should result in a slight predominance of 4- substitution.
This author feels that Walthew's consideration of the inductive effect of the chlorine, provides a more comprehensive explanation of the various reaction products.

**SYNTHESIS OF XANTHONES, THIOXANTHONES AND ACRIDONES**

Xanthones have been prepared by numerous techniques, involving treatment of a starting material with an acid, or heat or both. Perhaps the most widely used method is that of Ullmann\(^22\), in which a 2-chlorobenzoic acid and a phenol are coupled, by treatment with potassium carbonate and a trace of copper, at elevated temperatures, followed by reaction of the resultant 2-carboxydiphenyl ether with concentrated sulphuric acid.

\[
\begin{align*}
\text{Cl} & \text{OH} \\
\text{CO}_2\text{H} & \text{CH}_3 \\
\text{K}_2\text{CO}_3/\text{Cu}/\Delta \\
\text{CO}_2\text{H} & \text{CH}_3 \\
\text{H}_2\text{SO}_4 & \text{3-methyl xanthone}
\end{align*}
\]

Walthew also summarises a number of other xanthone syntheses, which typify the many methods available. The reactions include the Michael-Kostanecki reaction\(^24\), in which a 2-hydroxybenzoic acid is treated with phloroglucinol, and the Robinson-Nishikowa reaction\(^25\), in which a 2-hydroxybenzonitrile and phloroglucinol react to give an imino derivative, which is converted to the xanthone, by heating with sodium hydroxide. In the Asahina-Tanase reaction\(^26\), xanthone is produced by heating a diphenyl ether with oxalyl chloride in the presence of aluminum chloride.
Tanase himself developed a method\textsuperscript{27} involving the condensation of 2-hydroxybenzaldehyde with phloroglucinol methyl ether, in the presence of acetic and hydrochloric acids, and then catalytically hydrogenating and then oxidizing the intermediate. The Friedel-Crafts method has also been used. 2-Methoxybenzoyl chloride reacts with phloroglucinol trimethyl ether, in the presence of aluminum chloride to give a substituted 2, 2'-dihydroxybenzophenone, which was then converted to the completely demethylated xanthone, by the action of anhydrous aluminum chloride in benzene\textsuperscript{28}.

Walther\textsuperscript{21} pays special attention to the formation of xanthones in the pyrolysis of 2-halogenobenzoates, a reaction that was thought to proceed through an \textit{S}n\textsubscript{2} type mechanism, since at the time insufficient evidence had been collected for the involvement of the initially postulated benzyne intermediate\textsuperscript{29,30}.

In 1963, it was shown that a benzyne mechanism was involved\textsuperscript{31,32}. The reaction was repeated, with a substituent placed at the 4-position with respect to the benzoate group. This would give the 2,7-disubstituted xanthone(XXIVa).
Almost equal amounts of the 2, \(-\) isomer (C\(\text{IVa}\)) were isolated suggesting that the reaction proceeds through the thermolysis of the 2-halogenobenzoate ion, (XXII) to give an aryne.
\[
\begin{align*}
\text{(XXII)} & \quad R_1 CO_2 \quad \text{\Longleftrightarrow} \quad R_1 \quad \text{R}_1\text{CO} \\
\end{align*}
\]

(a) \( R_1 = H, \ R_2 = \text{Me} \)

(b) \( R_1 = \text{Me}, \ R_2 = H \)
If a 5-substituted potassium 2-chlorobenzoate undergoes the reaction, a similar result is obtained as from the 4-substituted compound. The product ratios are similar, but in each case a slight excess of the product, expected from the nucleophilic substitution mechanism, is obtained. One would therefore assume that nucleophilic substitution took some part in the reaction if it were not for the fact that thermolysis of the potassium salts of (XXIII) does not give xanthone\(^32\).

Further evidence for the intermediacy of benzynes in the thermolysis of 2-halogenobenzoates was provided by trapping the benzylene with tetracyclone\(^32\).

Another recent xanthone synthesis has been developed by Paquette and Stucki\(^33\). These authors, while studying enamine intermediates, treated salicaldehyde with 1-(N-morpholino)cyclohexene, in an inert solvent, such as benzene or hexane. The resultant viscous oil was oxidised with chromic oxide in pyridine, and then dehydrogenated to give xanthone in good yield.
Heating the sodium or potassium salt of a 2-hydroxy-2'-halogenobenzophenone, produces the corresponding xanthone. Walthew converted 2-bromo-2'-hydroxy-5'-methylbenzophenone to 3-methylxanthone, by treatment with potassium in dry liquid ammonia.

Little scission was observed (1.7%). Although the 2-bromo substituent should activate the carbonyl group towards addition of amide ion, the scission reaction is reduced in importance because the 2'-anionic group increases the electron density around the carbonyl carbon, making addition of amide ion much more difficult.

By analogy with the work of Bunnett and Hrutfiord, one would expect the slower benzyne formation to be able to compete under these conditions, giving intermediates such as (XXVI). The benzyne could then undergo attack by the internal nucleophile $0^-$ to give 3-methylxanthone or by the external nucleophile $\text{NH}_2^-$, to give 2-aminobenzophenone; the 2-substituted product should occur in preference to the 3-substituted product, because of the inductive electron donating effect of the $-\text{C(NH}_2)(\text{C}_6\text{H}_5\text{O})^-0^-$ substituent, and because of the possibility of the intermediate (XXVIII) taking part [page(24)]. Since the internal nucleophile $0^-$ is sterically well placed, this adds in preference to $\text{NH}_2^-$, especially in dilute solution. This is in accordance with the earlier work of Bunnett.
and Hrutfjord 14,15.

The products of this reaction could be explained adequately in terms of a nucleophilic substitution mechanism, despite the fact that products associated with an Sn2 mechanism were not observed from 2-chlorobenzophenone 18.

3-Bromo-2'-hydroxy-5'-methylbenzophenone also gives 3-methylxanthone under similar conditions. This strongly suggests that a benzyne mechanism is involved. Although a trace of 3-amino-2'-hydroxy-5'-methylbenzophenone was isolated from the reaction mixture, this was too small to enable anything definite to be said about the nature of the benzyne intermediate or intermediates that were involved. The mechanism of this xanthone synthesis is therefore not fully clear.

Less work appears to have been done on routes to thioxanthones and acridones, than on xanthones, perhaps because of the lesser importance of the former to natural product chemists.

Thioxanthone has been synthesised by two main routes. Prescott and Smiles 36 heated thiosalicylic acid and benzene in the presence of concentrated sulphuric acid to produce the thioxanthone.

\[
\begin{align*}
\text{SH} & + \text{CO}_2\text{H} \xrightarrow{\text{H}_2\text{SO}_4} \text{S} \\
& \text{O}
\end{align*}
\]

Mayer 37 first used the technique of Ullmann to prepare a 2-carboxy-diphenyl sulphide, and ring closed this intermediate to produce the required thioxanthone.
Acridones have been synthesised in reasonable yield by two routes. Formation of a 2-carboxydiphenylamine and ring closure with concentrated sulphuric acid produces acridones in good yield. This method, analogous to the thioxanthone synthesis of Mayer, is well described in Organic Syntheses.

Sternbach et al synthesised acridones from 2-amino-2'-fluoro- compounds.

The reaction must occur through a nucleophilic substitution mechanism, since the corresponding chlorine compounds do not undergo the reaction.

Walthew's xanthone syntheses are useful since the conditions used are unlike those in any other synthesis, applied for this ring system. If the synthesis could be applied to thioxanthones and acridones, it would be even more useful.
DISCUSSION
As a first step in widening the scope of the synthesis of xanthones (i.e. treatment of a bromohydroxybenzophenone with potassamide in liquid ammonia) the corresponding fluoro- and chloro- compounds were prepared and treated similarly. Besides increasing the number of available starting materials, these experiments were intended to give further insight into the mechanism of the reactions.

The range of products could be expanded, by replacing the hydroxyl group of the halogeno-2-hydroxybenzophenone with other nucleophilic species; thus treatment of a 2'- or 3'-halogeno-2-aminobenzophenone with potassamide in liquid ammonia might result in the formation of an acridone.

It is also possible that the corresponding methylated groups, e.g. methoxy-, could give the desired products, provided the benzophenone does not undergo the Haller-Bauer scission. These reactions, if successful, would further increase the range of starting materials for xanthone synthesis as well as making possible the synthesis of compounds, for which the demethylated reactants are not readily available. 2'- or 3'-Halogeno-2-methoxybenzophenones could thus be used as sources of xanthones, whilst the corresponding thiomethoxy compounds could be used for the synthesis of thioxanthones.
4-SUBSTITUTED BENZOPHENONES AND THE LOW TEMPERATURE HALLER-BAUER SCission

The work of Bunnett and Hutfliord\(^{18}\) [cf. page (18)] showed that a 3-halogenobenzophenone does not undergo the Haller-Bauer scission to any significant extent, when treated with potassamide in liquid ammonia. Under these conditions a 2-halogenobenzophenone undergoes scission; before such a compound can be used for a synthesis in this basic medium, a method of circumventing the scission reaction must be found.

It is thought that the carbonyl group, of a 2-halogenobenzophenone, is rendered susceptible to nucleophilic attack, by the halogen atom, which decreases the electron density at the carbon atom. Scission ought to be prevented, or at least reduced, by adding a substituent that will increase the electron density at the sensitive carbon atom.

A hydroxyl group would be an ideal substituent for this task, as it would lose a proton in a basic medium, to give a phenolate anion, which would increase the electron density at the carbonyl carbon; canonical forms, such as (XXIX), may be drawn.

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{Cl} & \quad \text{Cl} \\
\text{O} & \quad \text{\textit{\textdegreeO}} \\
& \quad \text{\textit{\textdegreeO}} \\
\text{\textit{\textdegreeO}} & \quad \text{\textit{\textdegreeO}}
\end{align*}
\]

(XXIX)

A methoxy group, or a thiomethoxy group should also have a similar effect; this would not be so large since a charge separation must be invoked, to draw canonical forms (XXX)(a) and (b), analogous to (XXIX).
To test this, the 2'-chloro-4'-substituted benzophenones were synthesised. Two routes were used, one involving the Friedel-Crafts reaction, and the other using the Friess rearrangement.

2-Chloro-4'-methoxybenzophenone was readily prepared by the Friedel-Crafts reaction. Anisole was treated with 2-chlorobenzoyl chloride and aluminum chloride, in carbon disulphide, to give 2-chloro-4'-methoxybenzophenone in good yield (75%), despite an attempt to demethylate it, by heating the crude reaction product to 150° for 1 hour, before hydrolysis and purification.

As this demethylation was unsuccessful, an attempt was made to prepare 2-chloro-4'-hydroxybenzophenone by the Friess reaction. This involves treatment of a phenolic ester with aluminum chloride, to produce a ketophenol. Phenyl 2-chlorobenzoate can give two products (XXXI) and (XXXII).
2-Chloro-2'-hydroxybenzophenone (XXXII) was of interest because treatment of this with potassamide in liquid ammonia should yield the parent xanthone. Also two disparate reports of this compound appear in the literature. Wulka\textsuperscript{41} claims to have prepared this material, m.p. 58-60\textdegree, by removing the t-butyl and methyl groups from a sample of 5-t-butyl-2'-chloro-2'-methoxybenzophenone, synthesised by a Friedel-Crafts reaction. Huskov and Naumov\textsuperscript{42} claim to have obtained a mixture of (XXXI)(56\%) and (XXXII)(32\%) by heating a mixture of aluminum phenoxide, 2-chlorobenzoyl chloride and aluminum chloride. Steam distillation was then used to separate a sample of (XXXII), m.p. 92\textdegree. The residue yielded (XXXI), m.p. 112\textdegree[cf. page (61)].

Phenyl 2-chlorobenzoate, prepared by heating 2-chlorobenzoyl chloride and phenol on a steam bath, was treated with aluminum chloride at 150\textdegree for 15 min. These high temperature conditions were chosen to encourage formation of (XXXII).\textsuperscript{40} The reaction gave (XXXI) only, in poor yield (10\%). A small amount of material, with a high \textit{R}_{f} value, was obtained by washing the crude reaction product with pentane, and evaporating the washings. Attempts to solidify the resultant pale yellow oil failed, possibly because the material was impure. Since compound (XXXII) was only of marginal interest to the main work, no further attempts were made to isolate it.

The Friess reaction was repeated at 60\textdegree, with nitrobenzene as a solvent. An improved, though still poor yield of (XXXII) (31\%) was obtained. Attempts were not made to improve the yields of (XXXII) further, as sufficient material was available for the subsequent investigation.
2-Chloro-4'-thiomethoxybenzophenone was prepared by the Friedel-Crafts reaction, using a procedure based on that described by R.F. Smith for 4-thiomethoxyacetophenone.\(^4\) The yield obtained was low (17.5\%), owing to the difficulties that arose during the purification of this material.

The three compounds were then treated with potassamide in liquid ammonia, under similar conditions to those used by Walthew, to synthesise xanthones. The results are summarised in Table(III).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Chloro-4'-hydroxybenzophenone</td>
<td>Starting material 93% (m.p. 106.5-111° cf. 119-121°)</td>
</tr>
<tr>
<td></td>
<td>Aniline 4.9.3%</td>
</tr>
<tr>
<td></td>
<td>Residue (neutral) 1.5%</td>
</tr>
<tr>
<td>2-Chloro-4'-methoxybenzophenone</td>
<td>Starting material 28%</td>
</tr>
<tr>
<td></td>
<td>Aniline - Present but not isolated</td>
</tr>
<tr>
<td></td>
<td>4-methoxybenzoic acid 60%</td>
</tr>
<tr>
<td></td>
<td>Residue 20%</td>
</tr>
<tr>
<td>2-Chloro-4'-thiomethoxybenzophenone</td>
<td>Starting material 12.4-27.3%</td>
</tr>
<tr>
<td></td>
<td>Basic tar 36%</td>
</tr>
<tr>
<td></td>
<td>4-thiomethoxybenzoic acid 51%</td>
</tr>
</tbody>
</table>

Most of the 2-chloro-4'-hydroxybenzophenone was unchanged, as predicted. The small amount of aniline isolated indicates that scission occurs to a small extent. The lowered melting point of the starting material reclaimed from the reaction could be explained readily if the other expected product of scission, 4-hydroxybenzoic acid, was present. Although thin layer chromatography indicated the presence of an impurity, in the reclaimed starting material, this impurity was not isolated.

The predictions made as to the behavior of the
methoxy- and thiomethoxy- compounds under these conditions were also found to be correct. Both compounds undergo scission to a lesser extent than 2-chlorobenzophenone.

Too many factors are involved in product determination for any information to be gleaned from these experiments, concerning the relative ease of scission of the methoxy- and thiomethoxy- compounds. The product ratios are dependent on the solubilities of the materials in liquid ammonia, and in the solvents used for isolation; the amount of reactant consumed is also very dependent on the presence of traces of water [cf. pages (69) and (87)].

Aniline was not isolated from either the methoxy- or the thiomethoxy- compound. Thin layer chromatography showed that the base fractions from both of these materials contained some aniline, although especially in the case of the thiomethoxy- compound, this was a relatively minor product. Both compounds would be expected to give basic products from side reactions. For example, the thiomethoxy-compound might gain NH$_2$ in place of MeS$^-$ in a nucleophilic displacement reaction, as the MeS$^-$ group is a good leaving group; alternatively a proton may be lost from a position adjacent to the thiomethoxy- group, followed by attack of the resultant anion on a neighbouring molecule, or loss of the MeS$^-$ group to give a benzyne, which can then react further.

One of the main side reactions for both compounds, would be the formation of aminobenzophenone, with loss of chloride ion through a benzyne intermediate.

The low melting point of 2-chloro-4'-thiomethoxy-benzophenone, and the subsequent problems in its isolation,
as in the synthesis of this compound, resulted in a low recovery of the pure material.

**THE ACTION OF POTASSAMIDE ON NITRO-COMPOUNDS**

Benzophenone does not undergo scission when treated with potassamide in liquid ammonia. 2-Chlorobenzophenone is readily split by this reagent. If the 2-halogeno substituent is replaced by another electron withdrawing group, such as a nitro-group, scission ought to occur. In view of the stability of 4-chlorobenzophenone to the Haller-Bauer scission, it is interesting to examine the reaction of 4-nitrobenzophenone under these conditions. This ketone was treated with potassamide in liquid ammonia, dried in situ. Most of the starting material was reclaimed unchanged after 4 hours. When the experiment was repeated, using liquid ammonia that had been pre-dried, then distilled, scission was found to have occurred, as benzoic acid (15.5%) was isolated. A small amount of solid, m.p. 152-60, was also isolated from the acid fraction. The infra-red spectrum showed this material was phenolic, as bands appeared corresponding to a hydroxyl group, and aromatic C-H bonds, but a band was not present in the carbonyl region.

Examination of the acid fraction by thin layer chromatography, showed the absence of 4-nitrobenzoic acid. The same technique showed that the neutral fraction contained little, if any, nitrobenzene, the compound that should be formed along with benzoic acid, in the scission reaction. Instead, this examination showed the presence of starting material, and another material; examination of the insoluble material (C) [cf. page (73)] showed that the main constituent was the new material found in the neutral
fraction. Crystallisation and chromatography of the combined neutral fraction and solid (C) gave unchanged starting material (16.5%) and a yellow solid, m.p. 199-200° (36%).

An infra-red spectrum of the new compound showed that a carbonyl-group, a nitro-group and an amino-group were present. A nuclear magnetic resonance spectrum indicated that all the protons present were attached to aromatic rings, except for those in the amino-group. Elemental analysis gave results that agreed with the proposed formula, C_{13}H_{10}N_{2}O_{3}, corresponding to a product obtained by nucleophilic displacement of a hydride ion, by an amino-group.

The mass spectrum was also in agreement with the proposed formula. It showed a parent peak corresponding to a molecular mass of 242. It also showed that the amino-group and the nitro-group were attached to the same benzene ring.

Examples of replacement of hydride ion from nitro-compounds, by nucleophiles appear in the literature. In every case the nucleophile adds at the 2- or 4- positions with respect to the nitro-group. By analogy, the aminated product obtained from 4-nitrobenzophenone should be 3-amino-4-nitrobenzophenone, since the carbonyl group blocks the position opposite the nitro-group; drawing a parallel with electrophilic substitution in aromatic systems, the electron withdrawing benzoyl-group should accelerate the substitution reaction, but not affect the point of attack of a nucleophile, since it is a much weaker electron withdrawing substituent than is the nitro-group.
Attempts were made to prepare a derivative of
the aminonitrobenzophenone. The compound was catalytically
reduced and treated with phenanthroquinone\(^{\text{50}}\). Its derivative
was isolated. An attempt to prepare a benzotriazine
derivative by treatment of the compound with cyanamide\(^{\text{50}}\),
also failed. Although these reactions fail to give an
isolable derivative, this author feels that the product is
3-\text{amino}-4-nitrobenzophenone, since the only other compound
consistent with the spectral data, 2-\text{amino}-4-nitrobenzophenone,
has been characterised\(^{\text{51}}\), and its melting point (172–3\(^{\circ}\)
is sufficiently different from that of the compound isolated
in this work, to prevent any confusion.

Examining the reactions of other aromatic nitro-
compounds under these conditions would fulfil a number of
purposes. If a simpler compound were used, and a similar
reaction occurred, a more easily characterised product might
be obtained. If the reaction were general for all aromatic
compounds, the reaction could provide a useful amination
procedure.

The first compound chosen for examination was
nitrobenzene. This, it was hoped, would give easily
characterised products. Also, if it reacted, an explanation
of the absence of this material from the reaction of
4-nitrobenzophenone, would present itself. Nitrobenzene
did react under these conditions to give a mixture of
phenols, as the main products; it was thought that phenol,
2-nitrophenol and 4-nitrophenol were present, but it was
not found possible to prove this experimentally. Although
this result was disappointing, in that amination does not
occur, it explains why nitrobenzene is not found in the
reaction products from 4-nitrobenzophenone, and provides a source for the phenolic material obtained.

3-Dinitrobenzene was chosen as the next candidate for the reaction. It was hoped that adding a nitro-group to nitrobenzene would make amination easier, allowing the reaction to go more completely. It was also hoped that the second nitro-group would encourage formation of solid products, rather than the oils obtained from nitrobenzene. Thin layer chromatography showed that the reaction product contained some unchanged starting material, together with two other materials, that were not removed by washing an ethereal solution of the reaction products with either dilute aqueous acid or base. If amination had occurred, two weakly basic amines, (XXXIII) and (XXXIV), were to be expected as products.

\[
\begin{align*}
\text{NO}_2 & \quad \rightarrow \quad \text{H}_2\text{N}^+ \quad \text{NO}_2 \\
\text{NO}_2 & \quad + \quad \text{NO}_2 \quad \text{NH}_2 \\
(\text{XXXIII}) & \quad + \quad (\text{XXXIV})
\end{align*}
\]

Chromatography separated these materials from the quantities of tar present, but did not separate the three materials, as their \( R_f \) values were too similar.

Finally 4-nitrotoluene was treated with the reagent. The only isolable product from the reaction was 4, 4′-dinitrobibenzyl (7.3%). This same compound was obtained by Bradley and Robinson, when they attempted to react piperidine with 4-nitrotoluene in the presence of sodamide. It seems that aromatic nitro-compounds react with
amide ion at low temperatures, in many ways, to give products that vary considerably with the reactant. This has been experienced with many other bases\textsuperscript{52}.

**SYNTHESSES OF XANTHONES**

A hydroxyl group placed into the 4'- (or presumably the 2'-) position of 2-chlorobenzophenone will greatly reduce the extent of the scission reaction. This explains why Walthew obtained 3-methylxanthone, by treatment of 2-bromo-2'-hydroxy-5'-methylbenzophenone with potassamide in liquid ammonia, and found very little attendant scission. The 2- and 3- chloro- and fluoro- compounds were prepared, to see if they would give 3-methylxanthone, on treatment with potassamide in liquid ammonia.

The halogeno-2'-hydroxy-5'-methylbenzophenones were prepared by the Friess rearrangement of the corresponding 4-cresyl halogenobenzoates. These esters were prepared by heating 4-cresol and the halogenobenzoyl chloride on a steam bath\textsuperscript{53}, or by the Schotten-Baumann reaction\textsuperscript{54}. The crude esters were then purified by crystallisation or sublimation, before being treated with aluminum chloride, to give the benzophenone. The yields and melting points of the esters and benzophenones are summarised in Table IV.

In contrast to Walthew's experience, the Friess reaction provided a reasonable route to the halogenohydroxybenzophenones. Sometimes, however, the reaction was unsuccessful. On such occasions a sticky tar was produced instead of the more customary golden foam. Thin layer chromatography showed that these tars contained much starting material.
3-Fluoro-2'-hydroxy-5'-methylbenzophenone could not be prepared by the Friedel reaction, despite repeated attempts. A sample was obtained from the Friedel-Crafts reaction using the same method as Walthew\textsuperscript{21,34}, but substituting methylene chloride as solvent for carbon disulphide.

As this compound proved difficult to isolate, due to its low melting point and adverse solubility properties, it was characterised as its 3'-bromo derivative.

These compounds were then treated with potassamide in redistilled liquid ammonia. The results obtained are summarised in Table V.

The products from these reactions vary markedly with traces of water in the reaction mixture. The first abortive attempt to cyclise 2-chloro-2'-hydroxy-5'-methylbenzophenone added evidence to this observation, made by Walthew\textsuperscript{21}.

Both chloro- compounds gave 3-methylxanthone in fair yield. While the 2-chloro and 2-bromo compounds could react through a mechanism involving nucleophilic substitution, the corresponding 3-substituted compounds must react through a benzene intermediate.

3-Fluoro-2'-hydroxy-5'-methylbenzophenone also gives 3-methylxanthone under these conditions. Aryl fluorides do not readily give benzynes, but often lose fluoride ion by nucleophilic displacement. This appears to be the case here. This viewpoint was strengthened, when the 3-fluoro compound was retrieved almost unchanged under the reaction conditions; thin layer chromatography demonstrated the absence of 3-methylxanthone from the reaction products.
Such a nucleophilic mechanism might provide some xanthone from the 2-bromo- and chloro-benzophenones, even though aryl bromides and chlorides are far more reluctant to become involved in this type of reaction than the corresponding fluorides; clearly this can not be too important, since the 2-bromo-compound is less affected than the 3-bromo-compound, under these conditions.

The yields of aminated products fluctuate wildly. This might seem strange at first since both bromo- and chloro-compounds should produce aminated benzophenones through the same intermediates. It appears that the formation of these products is very sensitive to traces of water; when Walthew first treated 2-bromo-2'-hydroxy-5'-methylbenzophenone with potassamide in liquid ammonia dried in situ, he was not able to isolate any amines at all. It was only when the ammonia had been predried and distilled through a silica gel column, that 2-amino-2'-hydroxy-5'-methylbenzophenone was isolable.

In each case the amine isolated was the one in which amide ion had added to the benzyne, if formed, at the position nearer to the carbonyl group, strengthening the view that the benzyne intermediate involved had had amide ion added to the carbonyl group \( XIX \) and \( XX \) or that the -\( \overline{O} \) group effectively neutralised the electron withdrawing powers of the carbonyl group.

Walthew proposed that the amine hydrochloride obtained from the 2-bromo-compound was the hydrochloride of the 2-amino-compound. He had two pieces of evidence for this. Comparison of the material with a sample of the
other conceivable product (3-aminobenzophenone hydrochloride) showed that they were not the same compound. More positive evidence was obtained by heating the compound. The material melted, then decomposed with evolution of gas and resolidified, to remelt at 338°C, the same temperature as that at which 3-methylacridione melts.55.

Attempts were made by this author to obtain a sample of 3-methylacridnone by heating the 2-amino-2'-hydroxy-5'-methylbenzophenone hydrochloride, both alone and in a high boiling solvent (N,N-dimethylformamide). The acridone was not isolated.

All that can be said about the scission reaction is that little, if any, occurred. Scission products were not obtained from either the chloro- or fluorobenzophenones.

A sample of 2-chloro-2'-methoxy-5'-methylbenzophenone was prepared from the keto-phenol, by the method of Hansen, Heisenheimer and Wachterowitz. This material was treated with potassium in liquid ammonia. Starting material was the only compound obtained from the reaction, together with quantities of tar. No 3-methylxanthone was detected.

The recovery of starting material was poor because of the problems that arose in its isolation. Even after purification by chromatography, a small amount of tar remained with the compound. This reduced the melting point of the material to below room temperature. Finally, a pure sample of the material was obtained by a low temperature crystallisation, carried out in such a way that only a small quantity of material separated on chilling. Even the sample obtained in this manner was slightly impure, as
its yellow colour testified.

SYNTHESES OF THIOXANTHONES

If the method for xanthone synthesis is to be applied to thioxanthones, 2-thiobenzophenones are required as intermediates.

4-Thiocresyl 2-chlorobenzoate was prepared, by treatment of 4-thiocresol with 2-chlorobenzoyl chloride in a basic solution. The resultant material was treated with aluminum chloride at 150°C, as in a Friedel reaction.

Thin layer chromatography showed the resultant tar contained at least nine materials, other than starting material. This method was abandoned. Instead an attempt was made to obtain 2-chloro-2'-thio-5'-methylbenzophenone by demethylation of its methyl thio-ether.

As a method for the demethylation of methyl thio-ethers could not be found in the literature, the technique for demethylation of 3-fluoro-2'-methoxy-5'-methylbenzophenone was applied. 2-Chloro-2'-thiometoxy-5'-methylbenzophenone (XXXV) was prepared by the Friedel-Crafts reaction. The attempt to demethylate this compound in situ gave a mixture from which 3-methythioxanthone (XXXVI) proved to be the only isolable product. This surprising result is a very useful one, since here we have a potential one stage synthesis of thioxanthones.

Two routes to this product appear plausible. Both require formation of 2-chloro-2'-thiometoxy-5'-methylbenzophenone as a primary product; although this compound is not isolated, the corresponding 3-chloro compound may be
isolated under similar conditions.

Without further experimentation it is impossible to say whether the nucleophilic substitution precedes or follows the demethylation. Since 3-methylthioxanthonne was not obtained, when 3-chlorobenzoyl chloride was used in place of the 2-chloro- compound, it seems that a nucleophilic substitution mechanism is involved, rather than a mechanism involving a benzyne intermediate.

A sample of 3-chloro-2'-thiomethoxy-5'-methylbenzophenone was prepared by the Friedel-Crafts reaction. A sample was treated with potassamide in liquid ammonia. The sample was totally consumed to produce 3-methylthioxanthonne (16.8%) and large quantities of tar. A small quantity of acidic material (ca. 0.2%) was obtained, which may be a result of scission. Scission products, if formed,
account for a very small amount of the material consumed.

The sample of 3-methylthioxanthone obtained in this reaction was more pure than that obtained from the Friedel-Crafts reaction. The material was lighter in colour (yellow as opposed to brown) and the spot produced on thin layer chromatography did not have the dark central area, found from the Friedel-Crafts product. The impurity in the Friedel-Crafts product was only present to a small extent as both this sample, and the sample from the benzyne route had identical melting points, and their infra-red spectra were identical.

SYNTHESIS OF ACRIDONES

Attempts were made to prepare 2'-amino-2-chloro-5'-methylbenzophenone by the method of Sternbach et al\textsuperscript{56, 57}. These workers prepared this compound by treating a mixture of 2-chlorobenzoyl chloride and 4-toluidine with zinc chloride at an elevated temperature, when a rearrangement similar to that in the Friess reaction occurs. One attempt at this reaction gave a small quantity of the required compound, isolated as the acyl derivative, but not enough material was produced to continue.

The alternative method for producing 2-amino-halogenobenzophenones, by ozonolysis of substituted indoles\textsuperscript{56}, was not attempted.
CONCLUSIONS

It is possible to prevent the low temperature Faller-Bauer scission of 2-halogenobenzophenones, by placing an electron donating group, such as a hydroxyl group, into a position in the non-halogenated benzene ring, from which it can increase the electron density at the carbonyl carbon atom. Methoxy- and thiomethoxy- groups will similarly reduce scission, but these groups encourage tar formation.

Xanthones can now be prepared from a variety of halogenobenzophenones, under conditions that will not damage acid or heat sensitive substituents. The reactions occur through a benzene mechanism or a nucleophilic substitution mechanism, depending on the reactant used.

The syntheses of thioxanthones by this technique looks promising, although more work appears to be required, to develop the synthesis. The one-stage synthesis via a Friedel-Crafts reaction also looks very promising. As only two general routes to thioxanthones are available, development of the reactions giving 3-methylthioxanthone could well prove useful. To do this, a method for demethylation of methyl thio-ethers would be helpful; this could prove useful in other situations.

It was not possible to prepare an acridone by this technique, as problems arose in the synthesis of the required intermediate (2-amino-2'-chloro-5'-methylbenzophenone). A new acridone synthesis might well be useful, since again, only two general methods are available for the synthesis of these compounds, one involving high temperature nucleophilic substitution and the other involving high temperature treatment with acid.
<table>
<thead>
<tr>
<th>HALOGEN CONSTITUENT</th>
<th>YIELD OF ESTER (°)</th>
<th>M.P. OF ESTER</th>
<th>YIELD OF BENZOPHONONE (°)</th>
<th>M.P. OF BENZOPHONONE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Chloro</td>
<td>60</td>
<td>69-72°</td>
<td>60</td>
<td>75 - 77°</td>
</tr>
<tr>
<td>3-Chloro</td>
<td>70</td>
<td>72-74°</td>
<td>43.5</td>
<td>70 - 71.5°</td>
</tr>
<tr>
<td>2-Fluoro</td>
<td>73</td>
<td>35-36°</td>
<td>36.0</td>
<td>72 - 73°</td>
</tr>
<tr>
<td>3-Fluoro</td>
<td>67</td>
<td>40.5-41.5°</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&quot;</td>
<td>75°</td>
<td>oil</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&quot;</td>
<td>-</td>
<td>-</td>
<td>70°</td>
<td>31 - 34°</td>
</tr>
</tbody>
</table>

a. This compound was obtained from the Schotten-Baumann reaction.\(^{54}\)

b. This compound was obtained from the Friedel-Crafts reaction.\(^{21}\)
<table>
<thead>
<tr>
<th>Halogen Substituent</th>
<th>Quantity of starting material (moles)</th>
<th>Starting Material</th>
<th>3-methyl-xanthone</th>
<th>Aminated Products</th>
<th>Scission Products</th>
<th>Residue (tars, oils etc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Br&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.018</td>
<td>30.2</td>
<td>14.2</td>
<td>2-NH₂ 18.7</td>
<td>2-methyl-5-hydroxy benzoic acid, 1.7</td>
<td>-</td>
</tr>
<tr>
<td>3-Br&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.0038</td>
<td>39.0</td>
<td>64.7</td>
<td>3-NH₂, 1.0</td>
<td>none isolated</td>
<td>-</td>
</tr>
<tr>
<td>2-Cl</td>
<td>0.018</td>
<td>21.0</td>
<td>40.0</td>
<td>2-NH₂, 10.7</td>
<td>&quot;</td>
<td>-</td>
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<tr>
<td>3-Cl</td>
<td>0.018</td>
<td>22.2</td>
<td>34.0</td>
<td>3-NH₂, 20.1</td>
<td>&quot;</td>
<td>27</td>
</tr>
<tr>
<td>2-F</td>
<td>0.013</td>
<td>50.0</td>
<td>58.0</td>
<td>none isolated</td>
<td>&quot;</td>
<td>20</td>
</tr>
<tr>
<td>3-F</td>
<td>0.0087</td>
<td>82.0&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
<td>none isolated</td>
<td>&quot;</td>
<td>5</td>
</tr>
</tbody>
</table>

<sup>a</sup> - Yields calculated as proportion of starting materials consumed.
<sup>b</sup> - Results from the work of Walthew.
<sup>c</sup> - Isolated as the 5'-bromo derivative.
<sup>d</sup> - Isolated as the hydrochlorides.
EXPERIMENTAL
Instrumentation and Techniques

1. Melting Points

These were measured on an "Electrothermal" melting point apparatus. The accuracy was checked with a number of pure organic compounds of known melting point.

2. Thin Layer Chromatography

A large variety of conditions were used. The solvent and absorbent are given in the text. Also the supporting material for the absorbent is given as this affects Rp values. Silica Gel 254 supported on microscope slides (glass) and on pre-prepared aluminum sheets (both supplied by E. Merck, Darmstadt, Germany) were used.

3. Infra-red Spectra

Unless otherwise stated, compounds were mixed with potassium bromide and compressed into thin disks, from which spectra were obtained on a "Perkin Elmer (model 237B)" grating infra-red spectrophotometer.

4. Nuclear Magnetic Resonance Spectra

The solvents used are indicated in the text. The spectra were obtained on a "Varian A60" nuclear magnetic resonance spectrometer.

5. Mass Spectra

The machine used to obtain these spectra was a "Bendix" time of flight small mass spectrometer.
6. Yields

For synthesis of benzophenones, yields are based on material used for the reaction. For potassamide liquid ammonia reactions, yields are calculated in terms of unrecovered starting material.
PREPARATION OF POTASSAMIDE IN LIQUID AMMONIA

1. Using liquid ammonia dried in situ

Commercial liquid ammonia was introduced into a 1 l. 3-necked flask, fitted with a cold finger condensor, and a mechanical stirrer. Small chips of potassium were added, until the mixture became permanently blue. A small crystal of ferric nitrate was added, followed by the requisite amount of potassium. The mixture was then stirred, until the intense blue colour faded.

2. Using redistilled liquid ammonia

Commercial liquid ammonia was introduced into a 1 l. 3-necked flask. Small chips of potassium or sodium were added, until the mixture attained a permanent blue colouration. A water bath was used to drive off the ammonia into a second 3-necked flask, fitted with a cold finger condensor, a mechanical stirrer, and if solids had to be added a right angled glass tube, so the solid could be added without opening the system.

The ammonia was condensed with solid carbon dioxide in methanol or acetone. A small chip of potassium was added. This always turned the mixture deep blue. A small crystal of ferric nitrate was added followed by the requisite amount of potassium. The mixture was then stirred until the blue colour gave way to the grey of potassamide.
SYNTHESIS OF 2-CHLOROBENZOPHENONES

2-Chloro-4'-methoxybenzophenone

A solution of 2-chlorobenzoyl chloride, prepared from 2-chlorobenzoic acid (7.8 g, 0.05 mole) and thionyl chloride (25 ml.), and anisole (4.8 g, 0.05 mole) in carbon disulphide (25 ml.), was added over 30 min. to a stirred suspension of aluminum chloride (5 g., 0.038 mole) in carbon disulphide (25 ml.). After stirring for 2 hrs., the solvent was evaporated off, and the mixture was heated to 150° for 1 hour. The red tar produced was taken up into ethanol (25 ml.) and poured into 2M hydrochloric acid (100 ml.), to produce a pink suspension. This was extracted with chloroform (100 + 50 + 50 ml.) to give solution(A) and an aqueous residue, that was discarded.

Solution(A) was washed with 1M sodium carbonate (3 x 50 ml.), to give chloroform solution(B); the basic washings were combined to give aqueous solution(C), that on acidification (2M HCl) gave 2-chlorobenzoic acid (0.8 g; 10%), m.p. 109-119° (cf. starting material 139-41°), not lowered on admixture with an authentic sample.

Chloroform solution(B) was extracted with 2M sodium hydroxide (4 x 50 ml.), to give organic solution(D). The washings were combined, acidified (2M HCl aq.) and extracted with chloroform (3 x 50 ml.), to give an aqueous solution that was discarded, and a solution(E), composed of the combined washings, which was washed (H2O), dried (MgSO4) and evaporated, to give a small amount of
brown oil, mainly composed of 2-chloro-4'-hydroxybenzophenone (t.l.c., toluene/silica GF254/glass).

Chloroform solution (D) was washed (H₂O), dried (MgSO₄) and evaporated to give after crystallisation (hexanes) 2-chloro-4'-methoxybenzophenone (7 g., 75%), m.p. 80-81°C (11.58, 80°C). (t.l.c., toluene/silica GF254/glass), i.r. v max. 2930, 2840 and 2560 (C-H stretch), 1658 (C=O stretch), 1595 (C=C stretch), 1570, 1505, (C=O stretch), 1468, 1250 (C-O-C asymm. stretch), 824 (C-H out of plane vib. subst. benzene), 760 and 695 cm⁻¹. N.M.R. spectrum (deuterochloroform): singlet 6.08 τ (CH₃-0-), quartet 2.16, 2.28, 3.00 and 3.14 τ (-CO-C₆H₄-0Kα), triplet 2.52, 2.60 and 2.68 τ (Cl-C₆H₄-CC-). Areas 3:4:4.5. The 4.5 is caused by superimposition of a chloroform peak (2.73τ) on the triplet.

2-Chloro-4'-hydroxybenzophenone

1. Phenyl 2-chlorobenzoate

Phenol (23.5 g., 0.25 mole) and 2-chlorobenzoyl chloride, prepared from 2-chlorobenzoic acid (25 g., 0.14 mole) and thionyl chloride (40 ml.), were heated on a steam bath for 5 hours. The resulting liquid was dissolved in chloroform (50 ml.), washed with 2M sodium hydroxide (50 ml.), water (50 ml.), and dried (MgSO₄). Evaporation yielded phenyl 2-chlorobenzoate (16 g., 43%), as a yellow oil, i.r. v max. 3090, 2935 and 2853 (C-H stretch), 1740 (ester C=O stretch), 1595 and 1492 (aromatic C=C stretch), 1435, 1285 (C-O ester stretch), 1243, 1192, 1161, 1095, 1035, 746 (C-Cl stretch) 720 and 683 cm⁻¹.
2. 2-Chloro-4'-hydroxybenzophenone

A. High Temperature Press Reaction. Aluminum chloride (5.2 g., 0.044 mole) was added to phenyl 2-chlorobenzoate (8.0 g., 0.034 mole) at 130°. The temperature rose to 150°, and was maintained at this for 15 min. The tarry brown foam produced was taken up in a small amount of methanol, and poured into ice (25 g.) and concentrated hydrochloric acid (20 ml.). The oil that separated was extracted into ether (50 ml.), and the aqueous layer was discarded. The ethereal solution was washed (H₂O), dried (MgSO₄), and evaporated to give a brown unsolidifiable oil (6.2 g.), I.R. ν max. 3300 (C-H stretch), 2960, 2940, 2918, 1650 (aromatic ketone C=O) 1630 (C-C stretch?), 1603 and 1500 (aromatic C=C stretch) 1295, 1155, 1030, 935, 855, 770, 745 cm⁻¹ (C-Cl stretch).

Thin layer chromatography (toluene/silica GP25%/glass; iodine chamber development) showed the presence of two main materials, one of which had a much higher Rf value than the other. This was removed by washing the bar with pentane; crystallisation (benzene) gave a brown solid (1.7 g.), m.p. 116-9°, that was dissolved in 2" sodium hydroxide (25 ml.), boiled with decolourising charcoal and acidified, to give a pink oil. The oil was extracted into chloroform (50 ml.). The aqueous solution was discarded; the organic solution was washed (H₂O), dried (MgSO₄) and evaporated to give 2-chloro-4'-hydroxybenzophenone (0.3 g.; 10%), m.p. 119-121° (lit. values vary from 118 to 128°), I.R. ν max. ca 3350 (C-H stretch), 2910 and 2850 (C-H stretch), 1650 (aromatic ketone C=O stretch), 1600 (C=C stretch), 1560, 1285, 1140, 1052.
(C-OH stretch), 930, 845, 753 cm\(^{-1}\) (C-Cl stretch).

N.M.R. (deuterochloroform) shows quartet 2.20, 2.36, 3.06, 3.21 \(\tau\) (Ar-CO-C\(_6\)H\(_4\)-OH), multiplet centred on 2.6 \(\tau\) (Cl-C\(_6\)H\(_4\)-CO-Ar).

B. Low temperature Friedel reaction. Aluminum chloride (5.9 g., 0.044 mole) was added to phenyl 2-chlorobenzoate (8.0 g., 0.034 mole) in dry nitrobenzene (40 g.) at 60\(^\circ\). After this temperature had been maintained for 60 min., the nitrobenzene was removed by steam distillation, to leave a brown oil, that solidified on cooling to a solid, m.p. 90 - 105\(^\circ\).

This was taken up into 2N sodium hydroxide (100 ml.) and boiled with decolourising carbon. The pink oil obtained after filtration and acidification, was extracted into chloroform (50 ml.). The organic solution was washed (H\(_2\)O), dried (MgSO\(_4\)) and evaporated to give an orange solid. Crystallisation (benzene) gave 2-chloro-4'-hydroxybenzophenone (2.5 g.; 31\%) as an orange solid, m.p. 118-120\(^\circ\), identical with the sample prepared previously (t.l.c., I.R., mixed m.p.).

2-Chloro-4'-thiomethoxybenzophenone

A solution of thioanisole (14.9 g., 0.12 mole) in methylene chloride (15 ml.) was added over a period of 15 min. to a well-stirred suspension of aluminum chloride (18 g., 0.135 mole) in a solution of 2-chlorobenzoyl chloride in methylene chloride (60 ml.), maintained at 0-5\(^\circ\). The 2-chlorobenzoyl chloride was prepared from 2-chlorobenzoic acid (28.1 g., 0.20 mole) and thionyl chloride (40 ml.).
The orange solution gave a precipitate after 10 min. and much hydrogen chloride was evolved. The reaction was allowed to proceed for a total of 90 min; the mixture was then poured onto ice (150 ml.) and concentrated hydrochloric acid (150 ml.). The organic layer, which turned red then yellow, was taken off. The aqueous phase was washed with chloroform (3 x 50 ml.). The organic solutions were combined, washed with water (50 ml.), 2M sodium bicarbonate solution (2 x 50 ml.) and water (50 ml.). The solution was then dried (MgSO_4) and evaporated to give a yellow oil. Chromatography on florisil (eluent: pentane : ether, 8:2), followed by low temperature crystallisation (methanol) gave 2-chloro-4'-thiomethoxybenzophenone (5.5 g., 17.5%) as colourless needles, m.p. 43-50°C (Found: C, 63.95; H, 4.20; Cl, 13.71%. C_{14}H_{11}ClO_S requires: C, 64.0; H, 4.20; Cl, 13.5%); ν max. 3062, 2926 (C-H stretch), 1790 (C=O stretch), 1667, 1592, 1435, 1298, 1197, 1099, 935 and 755 cm⁻¹.
ACTION OF POTASSAMIDE ON 2-CHLOROBENZOPHENONES

2-Chloro-4'-methoxybenzophenone

2-Chloro-4'-methoxybenzophenone (2.5 g., 0.01 mole) was added over 20 min. to a stirred solution of potassamide, prepared from potassium (0.8 g., 0.02 atom) and redistilled liquid ammonia (250 ml.). Stirring was continued for 4 hours. Ammonium chloride (2.5 g.) and ether (100 ml.) were then added to the brown mixture, and the ammonia was allowed to evaporate overnight.

Ether (100 ml.) and 2M hydrochloric acid (100 ml.) were then added to give ethereal solution (A) and an acidic solution (B). Ethereal solution (A) was then washed with 2M hydrochloric acid (2 x 50 ml.). These washings were combined with aqueous solution (B).

Ethereal solution (A) was then washed with 2M sodium hydroxide (3 x 50 ml.). These washings were combined to give basic solution (C).

The ether solution was then washed (H2O), dried (MgSO4), and evaporated to give a brown solid (1.4 g.). This was extracted with hot hexane to give a solution (D) and tar (E) (0.1 g.). Cooling solution (D) gave yellow crystals of 2-chloro-4'-methoxybenzophenone, m.p. and mixed m.p. 76-78.50; the identification was confirmed by thin layer chromatography (toluene/silica GF254/aluminum) and the infra-red spectrum.

Evaporating the mother liquor, extracting tar (E) and cooling gave 2-chloro-4'-methoxybenzophenone (0.2 g.), m.p. 73.5-76.50 (Total yield 0.7 g., 28.0%).
Evaporation of the solution gave a residue (0.6 g., 24%) shown by thin layer chromatography to contain starting material, tar and a high 2% value material, that might possibly be a trace of stop-cock grease.

Acid solution (B) was basified with 2N sodium hydroxide solution and extracted with ether (3 x 50 ml.). The ether solutions were combined to give solution (F); the aqueous layer was discarded.

Solution (F) was dried (Mg SO₄) and treated with dry hydrogen chloride, to give a brown tar. Thin layer chromatography (chloroform/silica GF254/ aluminium) showed this contained some aniline hydrochloride.

Acidification of alkaline solution (C) gave a pale pink precipitate (0.75g.), that on crystallisation (72°C) and treatment with decolourising charcoal, gave anisic acid (0.6 g., 60%), m.p. and mixed m.p. 183-4°C.

2-Chloro-4'-hydroxybenzophenone

2-Chloro-4'-hydroxybenzophenone (2.9 g., 0.012 mole) in dry tetrahydrofuran (100 ml.) was added to a stirred solution of potassium (1.4 g., 0.036 atom) and redistilled liquid ammonia (300 ml.). After 4 hours ammonium chloride (4 g.) was added followed by ether (100 ml.)

The ammonia was allowed to evaporate overnight. The organic solvents were then evaporated, and 2N hydrochloric acid (50 ml.) and ether (100 ml.) were added, to give ether solution (A) and acidic solution (B). Ether solution (A) was then washed with 2N hydrochloric acid (2 x 50 ml.). The washings were combined with aqueous solution (B).
Ether solution (A) was extracted with 2M sodium hydroxide (3 x 50 ml.). These aqueous washings were combined to give basic solution (C).

Ether solution (A) was washed (H₂O), dried (MgSO₄) and evaporated to give a brown solid (∼3 mg., 1.5%) that was not identified.

Basic solution (C) was acidified (2M HCl) and extracted with ether (3 x 50 ml.). The ethereal extracts were combined to give ether solution (D). The aqueous residue was discarded.

Ethereal solution (D) was washed (H₂O), dried (MgSO₄) and evaporated, to give a brown oil, that solidified on scratching to give an orange solid (2.7 g., 93%). Thin layer chromatography (chloroform/silica GF254/glass) showed this was mainly 2-chloro-4'-hydroxybenzophenone, with a second material. Crystallisation (benzene) gave a pink powder (0.5 g.) m.p. 113-121⁰, undepressed by mixing with an analytical sample of 2-chloro-4'-hydroxybenzophenone, but again giving two spots on thin layer chromatography. Recrystallisation gave a material (0.15 g.), m.p. 114-121⁰.

Basification (2M NaOH) of acid solution (B) gave a beige precipitate. This was extracted into ether (3 x 50 ml.). The ethereal extracts were combined to give solution (E). The aqueous solution was discarded.

Solution (E) was washed (H₂O), dried (MgSO₄) and evaporated to give a small amount of brown oil. Taking up in ether (5 ml.) and passing dry hydrogen chloride gas gave a brown solid (15 mg.) I.R. showed ν max 2880 and 2590 (N-H stretch), 2000, 1602 and 1498 (C=C stretch), 745 and 680 cm⁻¹ (C-H out of plane vibration).
(cf. aniline hydrochloride 2825, 2575, 2000, 1602, 1498, 745, 680 cm\(^{-1}\)). The mass spectrum showed \(m/z = 93(\text{C}_6\text{H}_5\text{NH}_2)^{+}\), 66 (loss of HCN), 46, 5 (Ph\(\text{NH}_2\)), 38 (HCl\(^{37}\)) and 36 (HCl\(^{35}\)).

**2-Chloro-4'-thiomethoxybenzophenone**

2-Chloro-4'-thiomethoxybenzophenone (4.0 g., 0.015 mole) was added to a solution of potassium (1.2 g., 0.030 atom) and redistilled liquid ammonia (500 ml.). The mixture was stirred for 4 hours; ammonium chloride (5 g.) and ether (100 ml.) were then added.

The ammonia was allowed to evaporate overnight. The resulting ethereal solution was washed with 2M hydrochloric acid (3 x 50 ml.), to give ether solution (A) and combined acidic extracts (B).

Aqueous solution (B) was neutralised (2M sodium hydroxide). The suspension produced was washed with ether (3 x 50 ml.). The ethereal washings were combined, washed (H\(_2\)O), dried (MgSO\(_4\)) and saturated with dry hydrogen chloride gas to give a tar (1.05 g., 36%) that was not identified, as attempts to crystallise from 2M hydrochloric acid failed.

Ethereal solution (A) was washed with 2M sodium hydroxide (3 x 50 ml.), leaving ether solution (C). The washings were combined to give basic solution (D). This was neutralised (2M hydrochloric acid) and washed with ether (3 x 50 ml.). The ethereal solutions were combined, washed (H\(_2\)O), dried (MgSO\(_4\)) and evaporated, to give 4-thiomethoxybenzoic acid (0.95 g., 51%), m.p. 190-20\(^\circ\).
Two crystallisations (aqueous ethanol) gave an analytical sample, m.p. 194-6° (lit. m.p. 192°, 189°) (Found: C, 56.94; H, 4.81; S, 19.2%. Calc. for C₉H₈S₂O₂: C, 57.14; H, 4.76; S, 19.05%); ν max. 1600, 1425, 1198, 1138, 1100, 843 and 764 cm⁻¹.

Ethereal solution (C) was dried and evaporated to give brown oil (1.1 g., 27.3%). Thin layer chromatography showed this contained one main material, plus tar and other impurities. Low temperature crystallisation gave 2-chloro-4'-thiomethoxybenzophenone (0.5 g.), m.p. and mixed m.p. 40-43°.
THE TREATMENT OF NITRO-COMPOUNDS WITH POTASSAMIDE

4-Nitrobenzophenone

4-Nitrobenzophenone (4.26 g., 0.0185 mole) dissolved in dry tetrahydrofuran (100 ml.) was added to a solution of potassamide, prepared from potassium (2.1 g., 0.054 atom) and liquid ammonia (300 ml.) dried in situ. The green mixture was stirred for 4 hours. Ammonium chloride (4 g.) and ether (200 ml.) were added. The ammonia was allowed to evaporate overnight. A yellow solution and a brown insoluble solid remained.

The mixture was extracted with 2M sodium hydroxide (100 ml.) to give ether solution (A) and a basic solution (B).

The ethereal solution (A) was extracted with 2M hydrochloric acid (100 ml.), to give ethereal solution (C) and an acid solution (D).

The basic solution (B) was acidified (2M HCl). A faint mistiness was produced. The solution was filtered to give a solid (0.1 g.) m.p. 115° upwards. Melting was not complete at 300°.

The acid solution (D) was made alkaline (2M NaOH). The brown solid produced was filtered off, washed (H₂O), and dried to give a solid (0.2 g.), m.p. starting at 142° but not complete at 300°, with some vapour evolved at 195°. This material contained some Fe(III). Dissolving in dilute hydrochloric acid and adding potassium ferrocyanide solution produced an intense Prussian blue precipitate.
Ethereal solution (C) was washed with water (50 ml.), dried (MgSO₄) and evaporated to give starting material (3.7 g., 87%), m.p. 132-5°, demonstrably the same by thin layer chromatography (chloroform/silica GF254/glass) and I.R., ν max. 3070, 2940, 2855 (C-H stretch) 1975-1920 (C-H bending), 1825 (C-H bending) 1650 (C=O stretch), 1605 and 1515 (C=C stretch), 1514 and 1360 (-NO₂ stretch), 850 (C-N stretch) and 755 cm⁻¹(C-H out of plane vibrations). Mixing with an authentic sample of 4-nitrobenzophenone did not lower the melting point.

(b) The experiment was repeated using the same quantities of reactants in redistilled liquid ammonia (500 ml.). The dark green-brown solution, produced by adding the ketones in dry tetrahydrofuran, to the potassiumhexafloururate solution, was stirred for 4 hours. Ammonium chloride (5.8 g.) and ether (100 ml.) were added. The ammonia and solvents were allowed to evaporate overnight.

Chloroform (100 ml.) and 2N sodium hydroxide (100 ml.) were added to the residue, to give an aqueous phase (A), a chloroform solution (B) and a dark yellow solid (C), suspended in the aqueous phase.

The organic phase (B) was washed with water (50 ml.), and dried.

The solid (C) was filtered from the aqueous phase (A), washed (H₂O) and dried, to give a yellow solid (0.8 g.), m.p. 185-190°. Crystallisation (toluene) gave a material (0.7 g.), m.p. 198-199°, that thin layer chromatography (toluene/silicaGF254/glass) showed to contain one main material (not starting material) plus
some tar, that remained on the base line. Recrystallisation
gave a yellow solid (0.55 g.), m.p. 200-1°, that analysed
correctly for x-amino-4-nitrobenzophenone (Found: C,
64.59; H, 4.04; N, 11.57%. C₁₃H₁₀N₂O₃ requires: C, 64.46;
H, 4.13; N, 11.57%). Mass spectrum showed peaks at
m/z=242 (Ph-CO-C₆H₄(NO₂)(NH₂)), 228 (PhOC₆H₃NO₂) 149
(O₂NC₆H₄CO), 105 (PhCO) and 77 (Ph-). I.R. ν max. 3340
(N-H stretch) 1660 (C=O stretch) 1620, 1595, 1580, 1530,
1505, 1503, 1485, 1348 (N-O stretch) and 848 cm⁻¹(C-N stretch).

Chloroform solution (B) was evaporated, to give
a pale yellow solid (2.5 g.), m.p. 120-140°. Thin layer
chromatography indicated that this contained starting
material, x-amino-4-nitrobenzophenone and at least two
other materials. Repeated crystallisation (toluene) gave
x-amino-4-nitrobenzophenone (0.3 g.), m.p. and mixed
m.p. 200-1°.

The mother liquors from both samples of the
aminonitrobenzophenone were combined, evaporated and
chromatographed on florisil (eluent; toluene) to give small
amounts of oils, 4-nitrobenzophenone (0.7 g., 16.5%),
m.p. and mixed m.p. 138-9°, and x-amino-4-nitrobenzophenone
(0.6 g.), m.p. 190-5°, that after crystallisation (toluene)
gave x-amino-4-nitrobenzophenone (0.5 g.; total yield 36%),
m.p. and mixed m.p. 199-200°.

Basic solution (A) was neutralised with 2M
hydrochloric acid, and extracted with chloroform (3 x 50 ml.)
to give organic solution (D). This was washed (H₂O), dried
(MgSO₄) and evaporated to give a brown solid (E) (1.1 g.),
m.p. 68-82°, containing nitrogen (sodium fusion), I.R. ν max.
3500-2500(O-H stretch), 1900, 1690(C=O stretch), 1450, 1105,
850 and 703 cm\(^{-1}\).

Solid (E) was extracted with boiling water (25 ml.), to produce a yellow solution and a brown tar. Decolourising charcoal was added, and the mixture was filtered, to give residue (F) and solution (G).

On cooling, solution (G) gave colourless plates of benzoic acid (0.3 g., 15.5%), m.p. and mixed m.p. 121-3\(^{\circ}\), I.R. \(\lambda_{\text{max.}}\) 3050-2500 (C-H stretch), 1710, 1690 (C=O stretch), 1608 and 1498 (C=C stretch), 1420, 1237, 935 (-CO\(_2\)H) and 703 cm\(^{-1}\) (mono-subst. benzene)

An ultra violet spectrum of the mother liquor showed two maxima, which completely obscured the spectrum of benzoic acid (expected \(\lambda_{\text{max.}}^{\text{H}_2\text{O}}\) 270, \(\lambda_{\text{max.}}^{\text{H}_2\text{O}}\) 270, 280). The residue (F) was extracted with hot chloroform (150 ml.), to give a solution that, after drying and evaporating, gave a yellow solid (H) (0.25 g., 5.9%), m.p. 75-85\(^{\circ}\). (A sample of fresh decolourising charcoal treated in this manner gave no solid). Crystallisation of solid (H) (chloroform) gave a small amount of an unidentified solid, m.p. 152-6\(^{\circ}\), I.R. \(\lambda_{\text{max.}}\) 3400-3600 (C-H stretch) 1600, 1555, 1450, 1072, 1025, 840, 722 and 675 cm\(^{-1}\).
ACTION OF POTASSAMIDE ON 4-NITROBENZOPHENONE

4-nitrobenzophenone
4.26 g. (0.0184 m.)

1. KNH₂/NH₃ (from 2.1 g. X; 500 cm³ NH₃) 4 hrs.
2. NH₄Cl (5.8 g.) Evap., overnight with ether (100 cm³)
3. CHCl₃ (100 cm³) /2M NaOH aq. (100 ml)

CHCl₃ Soln (B) Insoluble Solid (0.8 g.) Basic Soln (A)

1. Dry (MgSO₄), Evap.
2. Recryst. (Toluene)

4-nitrobenzophenone 0.7 g. (16.5%)

→ mother liquors ←

0.3 g. 0.5 g.
X-amino-4-nitrobenzophenone (35.6%)

Charcoal (F) Soln (G)

1. Extract with hot CHCl₃ (150 cm³)
2. Dry; evap.

0.25 g. (5.9%) 0.3 g. (15.5%) tars, etc. benzoic acid
5-Nitrotoluene

5-Nitrotoluene (2.75 g., 0.02 mole), in dry tetrahydrofuran (50 ml.) was added over 15 min. to a solution of potassium (2.34 g., 0.06 atom) and redistilled liquid ammonia (350 ml.). The purple mixture was stirred for 4 hours. Ammonium chloride (5 g.) and ether (100 ml.) were then added. The ammonia was allowed to evaporate overnight.

The brown mixture was washed with water (2 x 50 ml.) and then filtered to give a tar (0.6 g.), and an ethereal solution. The tar was extracted with hot glacial acetic acid, to give a black tarry residue (0.4 g., 14.5%) and a clear solution. This solution was diluted with water to produce 4, 4'-dinitrobibenzyl (0.2 g., 7.3%) as a brown amorphous powder, m.p. 176-178° (lit., 177° needles or slender prisms, m.p. 179.5°-180.5°); ν max. 2928 (C-H stretch), 1610 and 1601 (aromatic C=C stretch), 1503 and 1345 (N-O stretch), 1108, 853 (C-N stretch), 782, 748 and 695 cm⁻¹; mass spectrum, shows \( m/e = 272 \) (C₂N·C₆H₄·CH₂·CH₂·C₆H₄·NO₂), 136 (O₂N·C₆H₄·CH₂), 90 (C₆H₄·CH₂) and 46 (NO₂); N.M.R. spectrum (deuterochloroform) shows a singlet 7.03 γ (-CH₂·CH₂-) and quartet at 1.77, 1.91, 2.64 and 2.79 γ (-C₆H₄-) in ratio 2:2:1:1 (singlet).

The ethereal solution was washed (H₂O), dried (Na₂SO₄) and evaporated to give a brown solid (1.8 g., 65.5%). Thin layer chromatography (toluene/silica GF254/aluminum) showed that this contained starting material, 4, 4'-dinitrobibenzyl and some tar. This mixture was not separated into its constituents.
SYNTHESIS OF HALOGENOHYDROXYBENZOPHENONES

Acyl Halides

The halogenobenzoic acid was refluxed with an excess of thionyl chloride for at least 90 min. Excess thionyl chloride was then removed by distillation in vacuo to give the crude halogenobenzoyl chloride, that was used for the next stage of the sequence.

Preparation of Esters

Method (a) 4-Toly1 2-chlorobenzoate

4-Cresol (27 g., 0.2 mole) and 2-chlorobenzoyl chloride, prepared from 2-chlorobenzoic acid (25 g., 0.16 mole) and thionyl chloride (15 ml.), were heated on a steam bath for 5 hours. The reaction mixture was taken up in ether (50 ml.) and washed with 2M sodium hydroxide (3 x 50 ml.), water (3 x 50 ml.) and dried (MgSO₄). Evaporation of the ethereal solution gave a yellow oil, that solidified to a pale yellow solid. Crystallisation from methanol gave 4-tolyl 2-chlorobenzoate (23.5 g., 60%) as colourless flat needles, m.p. 68-72° (Lit., m.p. 53 68.8-69.8°); ν max. (nujol) 1740 (C=O stretch), 735 cm⁻¹ (C-Cl stretch).

4-Toly1 3-chlorobenzoate

3-Chlorobenzoic acid (13.8 g., 0.088 mole), treated in a similar manner with thionyl chloride (20 ml.) and then 4-cresol (13.4 g., 0.14 mole), gave a pink solid (19 g.), that after crystallisation from methanol, gave 4-tolyl 3-chlorobenzoate (15.1 g., 70%), m.p. 70.0-71.5°.

Recrystallisation of a small amount of this material gave colourless needles, m.p. 73-4° (lit., 68,53.
m.p. 72°, 75.1-76.0°), I.R. \( \gamma \) max. 2915 (C-H stretch), 1730 (C=O stretch), 1595 (C=C stretch), 1570, 1502 (C=C stretch) 1290, 1255 (C-O ester), 1198, 1070, 810 and 748 cm\(^{-1}\) (C-Cl stretch).

**4-Tolyl 2-fluorobenzoate**

2-Fluorobenzoic acid (10 g., 0.072 mole), heated in a similar manner with thionyl chloride (15 ml.) and 4-cresol (14.3 g., 0.15 mole) gave a brown solid, which was crystallised from ethanol and then from pentane to give **4-tolyl 2-fluorobenzoate** (11.9 g., 73%) as colourless crystals.

Further crystallisations (pentane) and drying **in vacuo** (3 x 10\(^{-2}\)mm. Hg.) gave an analytical sample, m.p. 35-6° (Found: C, 73.51; H, 4.87; F, 8.55%. \( \text{C}_{14}\text{H}_{11}\text{FO}_2 \) requires: C, 73.2; H, 4.78; F, 8.26%). An I.R. spectrum (liquid film) showed \( \gamma \) max. 3040, 2975 and 2865 (C-H stretch), 1745 (C=O stretch), 1615 and 1505 (C=C stretch), 1490, 1455, 1298, 1245 (C-O ester), 1198, 1170, 1118, 1082, 1055, 875 and 825 cm\(^{-1}\).

**4-Tolyl 3-fluorobenzoate**

3-Fluorobenzoic acid (5 g., 0.036 mole) treated in a similar manner with thionyl chloride (20 ml.) and 4-cresol (7.15 g., 0.076 mole), gave a pale brown oil, that solidified on standing. Crystallisation from methanol gave **4-tolyl 3-fluorobenzoate** (5.5 g., 67%), m.p. 40-3°, as colourless needles.

Sublimation of a small quantity of this material **in vacuo** (\( \sim \) 1mm. Hg) gave an analytical sample, m.p. 40.5-41.5°. (Found: C, 73.15; H, 4.77; F, 8.49%).
C\textsubscript{14}F\textsubscript{1}FO\textsubscript{2} requires: C, 73.2; H, 4.78; F, 8.26%.
An I.R. spectrum (liquid film) showed \( \gamma \) max. 3030, 3008 and 2900 (C-H stretch), 1745 (C=O stretch), 1600, 1508 and 1493 (C=C stretch), 1447, 1392, 1375, 1202, 925, 870, 799, 755 and 675 cm\(^{-1}\).

**Method (b)** The Schotten-Baumann Reaction

4-Toly1 3-fluorobenzoate

3-Fluorobenzoyl chloride, prepared from 3-fluorobenzoic acid (10 g., 0.072 mole) and thionyl chloride (25 ml.), was added dropwise to a solution of 4-cresol (7.7 g., 0.082 mole) and sodium hydroxide (2.85 g., 0.072 mole) in water (70 ml.), with vigorous shaking. After shaking for a further hour, the resulting oil was extracted into ether (3 x 50 ml.), washed (H\textsubscript{2}O) and dried (MgSO\textsubscript{4}). Evaporating the ether solution gave a yellow oil (16.2 g., 76%), mainly 4-tolyl 3-fluorobenzoate (I.R., t.l.c.).

The Friedlä Reaction

2-Chloro-2'-hydroxy-5'-methylbenzophenone

4-Toly1 2-chlorobenzoate (23.5 g., 0.095 mole) and aluminum chloride (16.2 g., 0.121 mole) were intimately mixed in a 500 ml. three-necked flask fitted with an air condensor and drying tube (CaCl\textsubscript{2}), and an internal thermometer. The flask was placed in an oil bath at 90°, and then heated until the internal temperature was 120°. The temperature was then slowly raised to 140°, and maintained there for 10 min. A vigorous reaction occurred that raised the temperature to 160° for a short while.

The resulting yellow foam was broken up, and added to a stirred mixture of ice (80 g.) and concentrated
hydrochloric acid (50 ml.). The yellow oil so produced was extracted with ether (3 x 100 cm³); the ethereal solution was washed (H₂O), dried (MgSO₄) and evaporated, to give a yellow oil that solidified on cooling and scratching. Crystallisation (hexane) gave 2-chloro-2'-hydroxy-5'-methylbenzophenone (14.2 g., 60%), as yellow-green prisms, m.p. 75-77° (lit.53, 64, 66, m.p. 76-77°, 77°). An i.r. spectrum showed ν max. 3450-2750 (O-H stretch), 2935 and 2855 (C-H stretch), 1640 (2-HOC₆H₄CO, C=O stretch), 1595 and 1480 (C=O stretch), 1430, 1298, 1250, 1222, 1135, 1055, 1026, 960, 865, 927, 780, 760 and 735 cm⁻¹ (C-Cl stretch).

3-Chloro-2'-hydroxy-5'-methylbenzophenone

4-Tolyl 3-chlorobenzoate (14 g., 0.057 mole), heated with aluminum chloride (9.5 g., 0.71 mole) in a similar manner, gave after crystallisation (hexane) 3-chloro-2'-methyl-5'-hydroxybenzophenone (6.1 g., 43.5%), m.p. 67.5-69.5° (lit.53 m.p. 70.5-71.5°).

Recrystallisation of a small amount gave yellow needles, m.p. 70.0-71.5°; ν max. 2910 and 2850 (C-H stretch), 1625 (2-HOC₆H₄CO, C=O stretch), 1603 and 1480 (C=O stretch) 1415, 1330, 1295, 1248, 1218, 1210, 968, 890, 830, 763, 737 (C-Cl stretch) and 703 cm⁻¹.

2-Fluoro-2'-hydroxy-5'-methylbenzophenone

4-Tolyl 2-fluorobenzoate (11 g., 0.065 mole), treated with aluminum chloride (9.5 g., 0.064 mole) in a similar manner, gave after crystallisation (hexane), 2-fluoro-2'-hydroxy-5'-methylbenzophenone (4.0 g., 30%) as yellow prisms, m.p. 72-3°.
Recrystallisation gave an analytical sample, m.p. 72-3°. (Found: C, 72.9; H, 4.76; F, 8.33%. \text{C}_{14}\text{H}_{11}\text{F}_2 \text{requires} C, 73.2; H, 4.78; F, 8.26%). An I.R. spectrum (liquid film) showed ν max. 3500-2600 (C-H stretch), 3025, 2923 and 2860 (C-H stretch), 1750 (C=O stretch), 942 and 868 cm\(^{-1}\). An N.M.R. spectrum (deuterochloroform) showed a singlet at 1.6\(\delta\), removed by addition of D\(_2\)O (-OH), a singlet at 7.8\(\delta\) (-CH\(_3\)), and multiple peaks around 2.7\(\delta\) (aromatic protons).

**Attempted Synthesis of 3-Fluoro-2'-hydroxy-5'-methylbenzophenone**

Repeated attempts to prepare 3-fluoro-2'-hydroxy-5'-methylbenzophenone from 4-tolyl 3-fluorobenzoate by the Friess Reaction failed. In all cases incomplete conversion occurred, to give unsolidifiable oily mixtures that could not be separated by distillation. These contained much starting material (t.l.c., I.R.).

**Friedel-Crafts Reaction**

**4-Methoxytoluene**

A sample of 4-methoxytoluene was prepared by the usual method\(^{65}\), to give a sample, \(\rho^2_0 \cdot 1.5099\), b.p. 175-7° (lit. \(\rho^2_0 \cdot 1.512\)\(^{65}\), b.p. 175° \(^{65}\)).

**3-Fluoro-2'-hydroxy-5'-methylbenzophenone**

A solution of 3-fluorobenzoyl chloride, prepared from 3-fluorobenzoic acid (12.5 g., 0.09 mole) and thionyl chloride (25 ml.), and 4-methoxytoluene (10.5 g., 0.086 mole) in methylene chloride (50 ml.), was added to a well-stirred suspension of aluminum chloride (11.43 g., 0.086 mole) in methylene chloride (50 ml.), over a period of 20 min.
After stirring for 150 min., the solvent was evaporated from the brown mixture, and the residue was heated to 150° for 90 min. The resultant golden foam was pulverised and added to a mixture of ice (150 g.) and concentrated hydrochloric acid (150 ml.). The yellow suspension produced was washed with ether (3 x 50 ml.). The aqueous residue was discarded.

The combined ethereal extracts were washed with saturated aqueous sodium bicarbonate solution (2 x 50 ml.) Acidification of the aqueous washings gave 3-fluorobenzoic acid (0.2 g., 1.6%), as colourless needles, m.p. and mixed m.p., 120-2°.

The ethereal solution was washed with 40% w/v aqueous sodium hydroxide solution (50 ml.). The bright orange-yellow solid that separated was filtered off. The two phase filtrate was discarded.

The precipitate was suspended in water (50 ml.) and the suspension was acidified with 2M hydrochloric acid. The resultant oil was extracted into ether (3 x 50 ml.). The combined ethereal extracts were washed (H₂O), dried (MgSO₄) and evaporated to give 3-fluoro-2'-hydroxy-5'-methylbenzophenone (13.8 g., 70%) as a pale yellow oil.

40% w/v sodium hydroxide solution was added dropwise until a thick orange precipitate was produced. Ether was added and the resultant paste was filtered. The solid was dried and split into two portions. One portion (4.2 g.) was crystallised from methanol to give orange granules (1.5 g.). The other portion (9.7 g.) was crystallised from methyl cyanide, to give yellow granules (5.9 g.). Both the original material and the crystallised
samples showed \( \nu \text{ max. } 3600-2800 \) (O-H stretch), 1625 (C=O stretch), 1582, 1525, 1455, 1404, 1338, 1328, 1246, 1203, 1177, 1143, 905, 834, 820, 774 and 720 cm\(^{-1}\).

A sample of this material was brominated, (The brominating mixture consisted of bromine (4 ml.) and potassium bromide (15 g.) in water (100 ml.), to give after crystallisation (ethanol), 3-bromo-3'-fluoro-2-hydroxy-5'-methylbenzophenone, as pale yellow needles, m.p. 130-1°C. (Found: C, 54.4; H, 3.27; Br, 26.2; F, 5.4%.

\( \text{C}_{14}\text{H}_{10}\text{BrF}_{2} \) requires: C, 54.4; H, 3.24; Br, 25.9; F, 6.16%.

The two portions of the sodium salt were recombined and suspended in 2M hydrochloric acid (100 ml.). The suspension was washed with ether (2 x 50 ml.) and then discarded. The ethereal washings were combined, dried (MgSO\(_4\)) and evaporated to give a yellow oil. The oil was distilled in vacuo to give 3-fluoro-2'-hydroxy-5'-methylbenzophenone (4.13 g.) as a pale yellow oil, \( n_D^{27.4} \) 1.5946, b.p. 70-74°C 15 mm., solidifying on standing as yellow prisms, m.p. 31-4°C (pure by t.l.c.; toluene/silica GF254/aluminum); \( \nu \text{ max. } 3025, 2925, 1630 \) (C=O stretch)

1610, 1585, 1480, 1445, 1338, 1300, 1275, 1250, 1215, 1193, 912, 888, 827, 782 and 715 cm\(^{-1}\). (Found: C, 73.15; H, 4.82; F, 8.29%. \( \text{C}_{14}\text{H}_{11}\text{FO}_{2} \) requires: C, 73.2; H, 4.78; F, 8.26%)

2-Chloro-2'-methoxy-5'-methylbenzophenone

2-Chloro-2'-hydroxy-5'-methylbenzophenone (15 g., 0.06 mole) was dissolved in 95% ethanol (100 ml.), and a solution of sodium hydroxide (4.7 g., 0.12 mole) in water (70 ml.) was added. Dimethyl sulphate (15.4 g., 0.12 mole) was added to the orange solution, with shaking.
After a short while a cloudiness developed. After standing for two hours, the solution had become colourless. A brown oil was present.

The solution was boiled to destroy excess dimethyl sulphate and to remove most of the ethanol. The mixture was then washed with ether (3 x 50 ml.) and discarded.

The ether washings were combined, washed (H₂O), dried (MgSO₄), and evaporated to give a pale yellow oil, that solidified on standing overnight in ice, to give 2-chloro-2'-methoxy-5'-methylbenzophenone (6.2 g., 40%) as colourless prisms, m.p. 46-48°, unaffected by crystallisation (hexane) or sublimation in vacuo (Found: C, 69.38; H, 5.06; Cl, 13.67%. C₁₅H₁₃ClO₂ requires: C, 69.2; H, 4.99; Cl, 13.6%). ν max. (nujol) 1650 (C=O stretch) 1618, 1595, 1261, 1157, 1122, 1058, 1030 and 820 cm⁻¹. N.M.R. (deuterochloroform): singlet 7.73 (3) singlet 6.47 (3) doublet 3.39 and 3.19 (1) and multiplet ~ 2.7 (6). For C₁₅H₁₃·CO·C₆H₃(CH₂O)(CH₃), peaks expected in the ratio 3:3:7.
ATTAINED SYNTHESIS OF 2-CHLOR-5'-METHYL-2'-THIOBENZOPHENONE

A solution of 2-chlorobenzoyl chloride, prepared from 2-chlorobenzoic acid (15.6 g., 0.1 mole) and thionyl chloride (20 ml.), and 4-thiomethoxytoluene (12.5 g., 0.09 mole) in carbon disulphide (50 ml.), was added to a well stirred suspension of aluminum chloride (10 g., 0.075 mole) in carbon disulphide (50 ml.) over one hour.

After the red mixture had been stirred for two hours, the solvent was evaporated off, and the tarry red residue was heated to 145° for one hour. The resultant red tar was suspended in 2M hydrochloric acid (100 ml.). The suspension was washed with ether (4 x 100 ml.). The ethereal washings were combined, washed with 2% sodium bicarbonate (100 ml.), water (100 ml.), and then dried (MgSO₄) and evaporated to give a brown solid.

This solid was chromatographed on florisil (Eluent: chloroform) to give after treatment with decolourising charcoal and crystallisation (95% ethanol), 3-methylthioxanthone (2.8 g., 16.5%) as brown prisms, m.p. 122-4°C (lit. 37, m.p. 123°C). Recrystallisation gave an analytical sample, m.p. 124-5°C (Pound: C, 73.5; H, 4.49; N, 14.3%). Calc. for C₁₄H₁₀O₃S: C, 74.0; H, 4.43; N, 14.16%). This sample was pure by thin layer chromatography (chloroform/silica GF254/glass): ν max. 1631 (C=O stretch), 1592, 1460, 1438, 1321, 1296 and 751 cm⁻¹; N.M.R. spectrum is discussed in Appendix I.
SYNTHESIS OF 4-TOLYL 2-CHLOROTHIOBENZOATE

2-Chlorobenzoyl chloride, prepared from 2-chlorobenzoic acid (12.7 g., 0.085 mole) and thionyl chloride (40 ml.), was added to the milky suspension, formed by adding 4-thiocresol (10.0 g., 0.08 mole) to a 10% aqueous sodium hydroxide solution (150 ml.). The mixture was shaken for 45 min. After the mixture stood for 5.5 hours, the granular solid present (18 g.; 85%) was filtered off, washed (H₂O) and dried.

Crystallisation (ethanol) gave an analytical sample of 4-tolyl 2-chlorothiobenzoate, m.p. 92.5-94.5°. (Found: C, 64.00; H, 4.19; S, 12.16; Cl, 13.56%.
C₁₄H₁₁ClO₃S requires: C, 64.00; H, 4.19; S, 12.19; Cl, 13.52%.) ν max. 1678 (C=O stretch), 1578, 1460, 1327, 1285, 1195, 939, 805, 765, 727 and 715 cm⁻¹.
A solution of methyl 4-tolyl sulphide (10 g., 0.073 mole) and 3-chlorobenzoyl chloride, prepared from 3-chlorobenzoic acid (15.6 g., 0.10 mole) and thionyl chloride (20 ml.), in carbon disulphide (50 ml.) was added over 15 min. to a suspension of aluminum chloride (10.9 g., 0.0815 mole) in carbon disulphide (50 ml.), with stirring. The mixture was stirred for a further 2 hours and then poured into a mixture of ice (100 g.) and concentrated hydrochloric acid (100 ml.), with vigorous stirring. The organic phase was separated, and the aqueous phase was washed with ether (3 x 50 ml.). The organic solution was combined with the ether washings, and the aqueous residue was discarded. The resulting solution was washed with water, sodium bicarbonate solution and then water; drying and evaporating gave a brown oil. Thin layer chromatography (toluene/silica GF 254/aluminum) showed that this material contained methyl 4-tolyl sulphide, a new material (the main constituent), and tar. Chromatography on florisil (60-100 mesh), using as eluents, pentane/ether (9:1) and then ether, gave three fractions. The first fraction, a small amount of oil, contained methyl 4-tolyl sulphide as the main constituent. The second fraction was a yellow oil that contained the bulk of the material. Distillation in vacuo gave 3-chloro-2'-thiomethoxy-5'-methylbenzophenone as a pale yellow oil (5.0 g., 26.3%), b.p. 85-90°C/15mm. This contained a small amount of 3-chlorobenzoic acid (0.05 g.) as suspended needles. This acid was removed by dissolving the benzophenone in chloroform (10 ml.), washing with
saturated aqueous sodium bicarbonate and then with water, drying ($\text{Na}_2\text{CO}_3$) and evaporating, to give a yellow oil that solidified on cooling and scratching to give pale yellow prisms.

Crystallisation from methanol gave an analytical sample as yellow prisms, m.p. 46.5-47.5° (found: C, 64.92; H, 4.80; Cl, 12.77; S, 11.57%. $\text{C}_{15}\text{H}_{13}\text{Cl}_{10}\text{S}$ requires: C, 65.1; H, 4.7; Cl, 12.3; S, 11.57%); ν max. 2920 (C-H stretch), 1660 (C=O stretch), 1570, 1468, 1425, 1302, 1297, 1246, 1208, 822, 814 and 757 cm$^{-1}$. The N.M.R. spectrum (deuterochloroform) showed singlets at 7.64 and 7.69 T; also many peaks in the 2.3 T region (aromatic protons).
ACTION OF POTASSAMIDE IN LIQUID AMMONIA ON HALOGENOHYDROXYBENZOPHENES AND RELATED COMPOUNDS

2-Chloro-2'-hydroxy-5'-methylbenzophenone

a) 2-Chloro-2'-hydroxy-5'-methylbenzophenone

(4.5 g., 0.018 mole) was added over 10 min. to a solution of potassamide, prepared from potassium (3.0 g., 0.07 atom), in liquid ammonia (300 ml.) dried in situ. The resultant pea-green mixture was stirred for 4 hours. Ammonium chloride (5 g.) and ether (100 ml.) were added, and the ammonia was allowed to evaporate overnight.

2M Hydrochloric acid (50 ml.) and ether (50 ml.) were added to the brown oil that remained, to give ether solution (A) and acid solution (B). Ethereal solution (A) was washed with 2M hydrochloric acid (2 x 50 ml.). The aqueous washings were combined with acid solution (B).

Ethereal solution (A) was extracted exhaustively with 40% w/v sodium hydroxide, until no more yellow solid was precipitated. The washings and precipitate were combined to give suspension (C).

The remaining ether solution was washed (H₂O), dried (MgSO₄), and evaporated, to give a pasty yellow solid, which crystallised from light petroleum (b.p. 100-115°C) to give 2-chloro-2'-hydroxy-5'-methylbenzophenone (0.1 g.) as pale yellow prisms, m.p. and mixed m.p. 74-76°C. I.R. and t.l.c. confirmed this.

Acid solution (B) was basified (1M sodium carbonate) and washed with ether (3 x 50 ml.). The aqueous phase, containing a suspended red solid (iron compounds?), was discarded.

The combined ether washings (D) were washed (H₂O) and dried (MgSO₄). Dry hydrogen chloride gas was passed through the solution to give a small amount of insolubilisable yellow
oil that was discarded.

Suspension (C) was acidified (20% hydrochloric acid), and washed with ether (3 x 50 ml.). The ethereal solutions were combined to give ether solution (E); the aqueous phase was discarded. Ethereal solution (E) was washed (H₂O), dried (MgSO₄) and evaporated to give 2-chloro-2'-hydroxy-5'-methylbenzophenone (3.1 g., total yield 71%) m.p. 73-5⁰, mixed m.p. 74-6⁰.

b) 2-Chloro-2'-hydroxy-5'-methylbenzophenone (4.13 g., 0.0167 mole) was added over 15 min. to a solution of potassaride, prepared from potassium (2.0 g., 0.051 atom), in redistilled liquid ammonia (300 ml.). The mixture was stirred for 4 hours. Ammonium chloride (5 g.) and ether (100 ml.) were added, and the mixture was allowed to stand overnight.

Ether (100 ml.) and 2M hydrochloric acid (50 ml.) were added to the dry residue, to give ether solution (A) and aqueous solution (B). Ether solution (A) was washed with 2M hydrochloric acid (2 x 50 ml.). The washings were combined with solution (B).

Ether solution (A) was then exhaustively extracted with 40% w/v sodium hydroxide. The washings were combined to give a brown basic solution (C).

The remaining ethereal solution was then washed (H₂O), dried (MgSO₄) and evaporated to give a pale yellow solid (1.5 g.), m.p. 113-7⁰, that exhibited a turquoise fluorescence in concentrated sulphuric acid. Crystallisation (hexane) gave 3-methylxanthone (1.1 g., 40%), m.p. 120-121⁰ (lit. 125.5⁰, 121⁰, 122-3⁰); ν max. 1650 (C=O stretch diaryl ketone), 1465, 1318 and 716 cm⁻¹.
The N.M.R. showed a doublet centered on 5.42\(\tau\) (CH\(_3\)-; this will be discussed later) and multiple peaks at 1.6, 1.7, 1.9 and 2.5\(\tau\) (aromatic protons).

Acidic solution (B) was neutralized (1M sodium carbonate). A brown oil separated. The mixture was washed with ether (3 x 50 ml.). The ethereal washings were combined to give ether solution (C); the aqueous residue was discarded. Concentrated hydrochloric acid (2 ml.) was added to ethereal solution (D). An oil separated. The ether was decanted, and the oil was taken up in 2M hydrochloric acid (100 ml.). The acid solution was neutralized (2M sodium carbonate) and extracted with ether (2 x 50 ml.), to give ether solution (E) and an aqueous phase that was discarded. Ether solution (E) was washed (H\(_2\)O) and dried (MgSO\(_4\)). Dry hydrogen chloride gas was passed through the solution to give a pale yellow solid (o.1 g.). An attempt to crystallise this material from 2M hydrochloric acid failed. The resulting solution was basified (1M sodium carbonate) and washed with ether (2 x 10 ml.). The ethereal washings were dried (MgSO\(_4\)) and dry hydrogen chloride was passed through to give 2-amino-2'-hydroxy-5'-methylbenzophenone, as pale yellow platelets, m.p. starting at 166.2\(^\circ\), decomposition starting at 195\(^\circ\), with gas evolution. Yellow needles started forming at 215\(^\circ\), with the reaction at its most vigorous at 235-240\(^\circ\), and complete at 250\(^\circ\). Charring occurred at about 360\(^\circ\).

An I.R. spectrum showed \(\nu_{\text{max.}}\) ~ 3495 and 3360 (NH\(_2\) symm. and unsymm. stretch), 2750 (v. broad; O-H stretch), 1633 (C=O stretch), 1480, 1342 (O-H in plane
deformation), 1245, 824, and 743 (C-Cl) cm⁻¹.

A mass spectrum did not show a parent peak; however peaks corresponding to C₆H₅·CO·C₆H₃(CH)(CH₃)
(M=211) and HCl (M=36, 38 in ratio 3:1) were observed.

Attempts to decompose this material thermally to give 3-methylacridone failed.

Basic solution (G) was acidified (concentrated hydrochloric acid) and extracted with ether (4 x 100 ml.).
The ethereal extracts were combined to give ether solution (F); the aqueous residue was discarded.

Ethereal solution (F) was washed (H₂O), dried (MgSO₄) and evaporated to give a red oil. Extraction of
this with light petroleum (b.p. 100-115°) gave a brown oil (G) and a solution (H). Cooling solution (H) gave brown
crystals (J) and mother liquor (K). Thin layer chromatography (chloroform/silica GF254/glass) showed both (J) and
(K) contained some starting material and oil (H) consisted mainly of tar. Fractions (G), (J) and (K) were recombined
and chromatographed on florisil (Eluents: light petroleum, b.p. 100-115°; toluene; chloroform; ethyl acetate). This
produced 2-chloro-2'-hydroxy-5'-methylbenzophenone (0.37 g., 21%) as pale yellow prisms, m.p. and mixed m.p. 75-77°.
The other four materials present were not isolated.

3-Chloro-2'-hydroxy-5'-methylbenzophenone

3-Chloro-2'-hydroxy-5'-methylbenzophenone (4.5 g., 0.018 mole) was treated with a solution of potassamide,
prepared from potassium (2.2 g., 0.056 atom), in redistilled liquid ammonia (300 ml.), and stirred for 4 hours.
Ammonium chloride (5 g.) and ether (100 ml.) were added.
The ammonia was allowed to evaporate overnight. The resulting solution was worked up as follows, to give starting material (1.15 g., 22.2%), 3-methylxanthone (1.0 g., 34%), 3-amino-2'-hydroxy-5'-methylbenzophenone, as the hydrochloride (0.77 g., 20.1%), and unisolated materials (tars, oils, etc. 0.95 g., 27%).

a) Ether solution of reaction products was washed with 2M hydrochloric acid (2 x 50 ml.). The washings were combined to give acid solution (A). (See flow sheet, page 92).
b) Acid solution (A) was neutralised (1M sodium carbonate) and washed with ether (2 x 50 ml.), to give solutions (D) and (E).
c) Ether solution (C) was exhaustively washed with 40% w/v NaOH to give solution (F) and suspension (G).
d) Ether solution (E) was washed with 2M hydrochloric acid (50 ml.) to give solutions (H) and (J) and solid (K).
e) Ether solution (F) was washed (H₂O), dried (MgSO₄) and chromatographed on florisil (Eluents: hexane; hexane:ether, 9:1; hexane:ether, 8:2), to give 5 fractions (L), (M), (N), (O) and (P).
f) Aqueous suspension (G) was neutralised (20% hydrochloric acid), and extracted with ether, to give solutions (Q) and (R).
g) Acid solution (H) was neutralised (1M sodium carbonate) and extracted with ether to give solutions (S) and (T).
h) Solid (B) was crystallised (2M hydrochloric acid), to give solid (U), after filtering tar from the hot solution.
j) Ether solution (R) was evaporated and chromatographed on florisil (Eluents: hexane; hexane:ether, 9:1, 8:2, 5:5) to give two fractions (V) and (W). Tar (X) remained on the column.
Action of Potassium on 3-Chloro-2'-hydroxy-5'-methylbenzophenone

Reaction Crude

- Acid Soln. (A)
- Brown Solid (B) filter off from ether-acid mixture
- Ether Soln. (C)

(b)

- Ether Soln. (E) Discard
- Aq. Soln. (Q) Ether soln. (R) Discard
- Yellow Solid (Y)
- Yellow Solid (U)

(d)

(c)

Aq. Soln. (D) Ether Soln. (J) Solid (K)

(e)

(f)

Aq. Suspension (G)

MHNO_P

(L M N O P)

Q

Discard

V W X

RSN

Discard

RSN

Discard
k) Ethereal solution (T) was dried and saturated with dry hydrogen chloride gas.

**Products**

(K) - A small amount of pale yellow prisms, giving an I.R. spectrum superimposable on that of (Y). Also identical on t.l.c.

(L) - A fluorescent oily liquid (0.07 g.), shown by t.l.c. to contain starting material and two other materials.

(M) - 3-Chloro-2'-hydroxy-5'-methylbenzophenone (0.94 g.), m.p. and mixed m.p. 69-71°.

(N) - T.l.c. showed this was 3-methylxanthone plus a trace of starting material (0.3 g.). Crystallisation from light petroleum (b.p. 100-115°) gave 3-methylxanthone (0.15 g.), m.p. and mixed m.p. 121-3°.

(O) - A pale yellow solid (1.1 g.). Crystallisation from light petroleum (b.p. 100-115°) gave 3-methylxanthone (0.8 g.) as very pale yellow prisms, m.p. and mixed m.p. 122-4°.

(P) - An orange oil (0.25 g.), with a smell of linseed oil. T.l.c. showed the presence of 3-methylxanthone, and two other materials with lower Rf values.

(U) - 3-Amino-2'-hydroxy-5'-methylbenzophenone (0.4 g.), as yellow prisms, changing to needles before melting at 163-6° (lit. 165-7°); ν max. 3450 (v.broad; N-H stretch), 2800 (v.broad; O-H stretch), 2590, 1626 (C=O stretch), 1594, 1483, 1347, 1254, 830 and 777 cm⁻¹.

(V) - 3-Chloro-2'-hydroxy-5'-methylbenzophenone (0.25 g.) as yellow prisms, m.p. and mixed m.p. 69.5-71°.

(W) - 3-Methylxanthone (0.05 g.) as pale yellow crystals, m.p. and mixed m.p. 122-123.5°.
(X)- Tar remaining on column. At least two bands were present, one red and one brown.

(Y)- Yellow prisms (0.2 g.), m.p. 155-7° after changing to needles. Recrystallisation (2M hydrochloric acid), followed by sublimation, gave 3-amino-2'-hydroxy-5'-methylbenzophenone, m.p. 159-164°, after changing to needles, v max. 3450 (v broad), 2900 (v broad), 2600, 1628, 1594, 1485, 1347, 1254, 830 and 777 cm⁻¹.

2-Fluoro-2'-hydroxy-5'-methylbenzophenone

2-Fluoro-2'-hydroxy-5'-methylbenzophenone

(3.0 g., 0.013 mole) was added to a solution of potassamide, prepared from potassium (1.6 g., 0.041 atom), in redistilled liquid ammonia (300 ml.). The grey mixture was stirred for 4 hours. On addition of ammonium chloride (5 g.) a bright yellow colouration was produced. Ether (100 ml.) was added and the ammonia was allowed to evaporate overnight.

The ethereal solution (A) of the reaction products was worked up as shown below to give 2-fluoro-2'-hydroxy-5'-methylbenzophenone (1.5 g., 50%), 3-methylxanthone (0.8 g., 58%) and tars, oils, etc. (0.3 g., 20%).
Action of Potassamide on 2-Fluoro-2'-hydroxy-5'-methylbenzophenone

Ether Solution (A)
- wash with 2M HCl (2 x 50 ml.)

Ether Soln. (B)
- Exaustively extract with 40% w/v aq. NaOH

Ether Soln. (D)
- 1. Wash (H₂O)
- 2. Dry (MgSO₄)
- 3. Evaporate

3-Methylxanthone
- m.p. and mixed m.p. 123.5-124.5° (0.2g)

Ether Soln. (J)
- Aq. Soln. (K)
- 1. Acidify (conc. HCl)
- 2. Ether wash (3 x 100 ml)
- Discard

Ether Soln. (F)
- Aq. Soln. (G)
- 1. Dry (MgSO₄)
- 2. Evaporate
- Discard

Trace of brown solid (L)
(starting material + tar by t.l.c.)

Ether Soln. (E)
- Aq. Washings (E)
- 1. Acidify (conc. HCl)
- 2. Ether wash (3 x 50 ml)

Ether Soln. (C)
- Acid Soln. (C)
- 1. Make alkaline (M Na₂CO₃)
- 2. Wash with ether (3 x 50 ml)

(3) Starting material + 3-methylxanthone (0.1g)

(M) Pale yellow prisms (1.5g) m.p. & mixed m.p. 69-70° (2-fluoro-2'-hydroxy-5'-methylbenzophenone)

(N) Starting material + 3-methylxanthone (0.1g)

(O) 0.95g. material, that after crystallisation from light petroleum (b.p. 100-115°) gave 3-methylxanthone (0.9g.), colourless needles, m.p. & mixed m.p. 121-3°

(P) Green tar (0.2g).

(M) (N) (O) (P)
3-Fluoro-2'-hydroxy-5'-methylbenzophenone

3-Fluoro-2'-hydroxy-5'-methylbenzophenone (2 g., 0.0087 mole) in dry tetrahydrofuran (50 ml.) was added to a solution of potassamide, prepared from potassium (1.02 g., 0.026 atom) and redistilled liquid ammonia (250 ml.).

The green mixture was stirred for 4 hours, 20 minutes, then ammonium chloride (3 g.) and ether (50 ml.) were added, and the ammonia was allowed to evaporate overnight.

2M Hydrochloric acid (50 ml.) was added, and the organic solvents were evaporated off. The resultant aqueous suspension was washed with ether (3 x 50 ml.) to give aqueous solution (A) and combined ether washings (B).

Organic solution (B) was washed with 40% w/v aqueous sodium hydroxide (50 ml.), to give a pale yellow precipitate, that was filtered off, washed (H₂O) and brominated to give, after crystallisation (ethanol), 3-bromo-3'-fluoro-2'-hydroxy-5'-methylbenzophenone, (2.2 g., 82%), m.p. and mixed m.p. 129-31°.

The mother liquor, and the residual ether solution were examined for 3-methylxanthone (t.l.c.). None appeared to be present.

Aqueous solution (A) was basified (2M sodium hydroxide) and washed with ether (2 x 50 ml.). The ethereal washings were combined, dried (MgSO₄) and saturated with dry hydrogen chloride gas, to give a pale yellow oil (0.1 g.), that would not crystallise from dilute hydrochloric acid. The material was shown to be 3-fluoro-2'-hydroxy-5'-methylbenzophenone (I.R. and t.l.c.)
2-Chloro-2'-methoxy-5'-methylbenzophenone

2-Chloro-2'-methoxy-5'-methylbenzophenone
(5.2 g., 0.02 mole) was added to a solution of potassamide, prepared from potassium (2.3 g., 0.06 atom) and redistilled liquid ammonia (500 ml.). After stirring the mixture for 4 hours, ammonium chloride (5 g.) and ether (100 ml.) were added. The ammonia was then allowed to evaporate overnight.

Ether (100 ml.) and 2M hydrochloric acid (100 ml.) were added. The ethereal solution (A) was washed with 2M hydrochloric acid (3 x 50 ml.). The acid washings were combined to give aqueous solution (B). A small amount of tar was present.

Solution (B) was basified (2M sodium carbonate) and washed with ether (3 x 50 ml.). The aqueous phase was discarded and the ether washings were combined to give organic solution (C). This was washed with 2M hydrochloric acid (3 x 50 ml.). The organic phase was discarded, and the combined washings were neutralised (2M sodium carbonate) and washed with ether (3 x 50 ml.). The ether washings were combined, washed (H₂O), dried (MgSO₄), and saturated with dry hydrogen chloride gas. A brown oil separated (0.3 g., 5.8%). The ether was decanted, and the oil was dried in vacuo. Thin layer chromatography showed the presence of one main material, possibly starting material. An I.R. spectrum showed this material did not contain an amine group.

Ether solution (A) was dried (MgSO₄) and evaporated to give a brown oil. Examination by thin layer chromatography showed this contained much tar and some
starting material. Neither 2-chloro-2'-hydroxy-5'-methylbenzophenone nor 3-methylxanthone appeared to be present.

The material was chromatographed on florisil (60-100 mesh) to remove the tar. The chromatographed material was taken up in methanol, and chilled in a solid carbon dioxide/methanol bath, to give 2-chloro-2'-methoxy-5'-methylbenzophenone (0.2 g.) as pale yellow prisms, m.p. and mixed m.p. 44-7°C.
3-Chloro-2'-thiomethoxy-5'-methylbenzophenone

3-Chloro-2'-thiomethoxy-5'-methylbenzophenone (1.38 g., 0.005 mole) was added to a solution of potassamide, prepared from potassium (0.6 g., 0.015 atom) in redistilled liquid ammonia (200 ml.). The mixture was stirred for 4 hours; ammonium chloride (2.5 g.) and ether (100 ml.) were then added and the ammonia was allowed to evaporate overnight.

The residual material was worked up in the usual manner, to give acidic, basic and neutral fractions.

The acid fraction yielded a small amount of unidentified brown solid (ca. 3 mg., 0.2%).

The base fraction gave a brown oil (0.2 g., 14.3%) containing one main material with two impurities (t.l.c.; chloroform/silica GF254/aluminum). One of the trace materials had the same Rf value as aniline. Attempts to purify the main constituent as the hydrochloride, by crystallisation from dilute hydrochloric acid or by sublimation in vacuo failed.

The neutral fraction (1.13 g.) provided 3-methylthioxanthone (0.2 g., 16.8%) as pale yellow prisms, m.p. and mixed m.p. 123-40°, after chromatography on Florisil (Eluent: chloroform). The remaining material eluted from the column as a tar (0.9 g., 65.2%).
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APPENDIX
APPENDIX

The Nuclear Magnetic Resonance Spectra of
3-Methylxanthone and Related Compounds

3-Methylxanthone (I) was prepared a number of
times during the course of the preceding study. While
routine spectra were being obtained, it was observed that
the methyl group of 3-methylxanthone gave rise to a doublet
at 7.52 Υ (149 c.p.s.), instead of the expected singlet.
The splitting was too small to measure accurately
(\(\mathcal{J} = 0.2\) 0.5 c.p.s.). Irradiation with a field corresponding
to that absorbed by the methyl protons simplifies the
spectrum in the region around 1.23 Υ (490 c.p.s.).
Irradiation with a radio freq. field, corresponding to the 1.23 Υ
absorption produces a single methyl peak.

\[
\begin{align*}
&\text{O} & & \text{Me} \\
&\text{O} & & \text{Me} \\
&\text{(I)} & & \text{(II)}
\end{align*}
\]

Examination of the methyl peak in a 100 Mc. field
gives no additional information. When this peak is expanded,
it appears a broad hump, with a number of shoulders.

2- and 4- Methylxanthones were prepared and
their spectra were examined. 2-Methylxanthone (II) showed
an absorbance at 7.17 Υ (146 c.p.s.), corresponding to the
methyl absorption; this peak appeared to be rather broad, but
if splitting occurred, the coupling constant was even
smaller than that for (I). Double irradiation (\(+276.6\) c.p.s.)
showed that splitting did occur and that it was caused by
protons that absorbed at 2.95 Υ (423 c.p.s.). The 100 Mc.
spectrum showed the presence of a very broad singlet.
4-Methylxanthone (III) gave a triplet centred at 7.09 T (174.5 c.p.s.). The splitting again was very small \( J = \text{ca.} \ 0.4 \text{ c.p.s.} \). Spin decoupling showed that the protons causing the splitting absorbed at 3.02 T (420 c.p.s.). The 100 Mc. spectrum showed the presence of a triplet, but unfortunately separation was again not great enough for measurement.

Finally the spectrum of 3-methylthioxanthone was obtained. A distinct doublet appeared at 7.57 T (145.5 c.p.s.) corresponding to the methyl group \( J = \text{ca.} \ 0.8 - 0.9 \text{ c.p.s.} \). Spin decoupling showed that the splitting was caused by protons absorbing at 1.62 T (503 c.p.s.). The 100 Mc. spectrum clearly indicated the presence of this doublet; shoulders on the two main peaks suggest that further splitting was occurring.

Insufficient information is available regarding the nuclear magnetic resonance spectra of xanthones and related compounds to allow a statement to be made, as to which of the aromatic protons is causing the splitting of the methyl groups. The spectrum of xanthone has been analysed\(^1\), but the system is too complicated to allow extrapolation, using the technique instigated by Shoolery. The splittings were considered to be too small to warrant further investigation.

Experimental

2-(3-methylphenoxy)-benzoic acid (V), was prepared by the method of Ulman and cyclised\(^2\), to give, after chromatography on 60-100 mesh Florisil (eluents: hexane, hexane:ether, 9:1, 8:2); 2-methylxanthone, \(\text{m.p. } 95-96.5\degree\text{C} (\text{lit. } 96.5\degree\text{C}), \nu_{\text{max}}. 1652, 1470, 1419, 1340, 1337, 1233, 1220, 1185, 1171, 955, 928\) and 765 cm\(^{-1}\), and 4-methylxanthone, \(\text{m.p. } 113-113.5\degree\text{C} (\text{lit. } 114\degree\text{C}), \nu_{\text{max}}. 1652, 1600, 1342, 1303, 1251, 1240, 928, 775\) and 765 cm\(^{-1}\). The materials were pure [thin layer chromatography (toluene/silica GF254/glass)].

The N.R.R. spectra were obtained on a Varian A160 machine. The spectra obtained at 100 Wc were obtained on a Varian HA100 nuclear magnetic resonance spectrometer.

\[\begin{align*}
\text{Cl} & \quad \text{CO}_2\text{H} \\
\text{Me} & \quad \text{OMe} \\
\end{align*}\]

\[\text{CO}_2\text{H} \quad \text{Me} \quad \text{(V)} \rightarrow (\text{II}) + (\text{III})\]